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

Short title: ART and anal HPV-related disease: a meta-analysis

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SUMMARY

BACKGROUND: The effect of antiretroviral therapy (ART) on the natural history of anal HR-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 (PLHIV).

METHODS: We searched Medline and Embase for studies from 1 January 1996 to 30 October 2019 that reported the association of HIV-related exposures (ART, HIV-RNA plasma viral load [PVL] and nadir or current CD4+ cell count) with outcomes of anal HR-HPV prevalence, incidence or persistence or prevalence, incidence, progression or regression of anal histological/cytological abnormalities, or anal cancer incidence. We assessed the risk of bias of included studies using the Newcastle-Ottawa scale. We performed random-effects meta-analyses; heterogeneity was examined using I^2 statistic.

FINDINGS: 122 studies were included comprising 417,006 PLHIV (19%, 44% and 5% women, men-who-have-sex-with-men; men-who-have-sex-with-women, respectively; 32% of studies did not stratify findings by gender and/or sexual orientation).

PLHIV taking ART had 35% lower HR-HPV prevalence compared to ART-naïve (crude Odds Ratio[cOR]=0.65, 95%CI:0.54-0.79; I^2=12.1%) in 18 studies and prolonged ART use was associated with a 10% reduction in HR-HPV prevalence in two studies (per year: aOR=0.90, 95%CI:0.85-0.95, I^2=0.0%). PLHIV with undetectable PVL had lower HSIL/AIN2+ prevalence compared to those without (cOR=0.84, 95%CI:0.72-0.98, I^2=0.0%) in 16 studies, particularly if sustained for >1 year (cOR=0.62, 95%CI:0.47-0.81, I^2=0.0%).

ART was not associated with anal cancer incidence when adjusted for years living with HIV in 3 studies (aHR=1.11, 95%CI: 0.68-1.80, I^2=0.0%), but ART users with sustained undetectable HIV PVL had 44% lower risk of anal cancer compared to those without (aHR=0.56, 95%CI:0.44-0.70, I^2=0%) and for each 100 cells/µl increase in nadir CD4+ count, there was a 40% decrease in anal cancer incidence (cHR=0.60, 95%CI:0.46-0.78, I^2=21.7%).

INTERPRETATION: Effective ART use and early initiation at higher nadir CD4+ may reduce anal HR-HPV and anal cancer risk.

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Key words*:* HIV, high-risk human papillomavirus (HPV), anal intraepithelial neoplasia (AIN), anal squamous intraepithelial lesions (ASIL), anal cancer, antiretroviral therapy (ART), plasma viral load (PVL), CD4+ cell count

RESEARCH IN CONTEXT

Evidence before this study

People living with HIV (PLHIV) are more at risk to acquire human papillomavirus (HPV) infections compared to the general population. These infections are more likely to persist leading to the development and progression of anal precancerous lesions and cancer. Improved access to antiretroviral therapy (ART) has increased the life expectancy of PLHIV, but the effect of ART on the natural history of oncogenic or high-risk (HR) HPV infections and anal precancerous lesions is not well established.

We searched Medline and Embase databases for all available publications in the English language from 1 January 1996 to 30 October 2019 using search terms for HPV, squamous intraepithelial lesions (SIL), anal intraepithelial lesions (AIN), anal cancer and antiretroviral therapy (ART, HAART) and HIV. Studies were eligible if they reported the impact of ART on the detection, incidence and persistence of HR-HPV infections identified in the anal canal, the prevalence and incidence of anal precancerous lesions and the incidence of anal cancer. We identified 122 studies among 130 discrete populations and 417,006 PLHIV (19%, 44% and 5% women, men-who-have-sex-with-men [MSM]; men-who-have-sex-with-women [MSW], respectively; 32% of studies did not stratify findings by gender and/or sexual orientation). We were able to evaluate the association of ART, HIV plasma viral load and markers of immune response such as CD4+ T-cell counts (the lowest recorded, or nadir and the current, or CD4+ count measured at same time as the outcome) with the different outcomes explored. We investigated potential sources of heterogeneity and publication bias using standard statistical approaches.

Added value of this study

We identified studies from North America (41%), Europe (31%), Asia (15%), Latin America (8%), Africa (3%) and Australia (2%). MSM were the most widely studied population. We confirmed the high detection levels of HR-HPV infections in the anal canal, being higher among MSM (69%) followed by women (44%) and MSW (29%).

Use of ART was associated with up to 35% reduction in anal HR-HPV compared to those not on ART, once characteristics of the immune status of the PLHIV were considered. Each additional year on ART was associated with a 10% reduction in anal HR-HPV infection. Further, each 100 cells/μl increase in current CD4+ count was associated with an 11% decrease in anal HR-HPV prevalence.
PLHIV with undetectable HIV plasma viral load that was sustained over time had a 38% lower risk of high-grade anal precursor lesion (HSIL-AIN2+) prevalence and a 44% lower risk in anal cancer compared to those with detectable HIV plasma viral load, or those with non-sustained undetectable HIV plasma viral load. PLHIV who started ART at a higher nadir CD4+ count (≥200 cells/μl) also had a 40% lower risk of HSIL-AIN2+ prevalence and for each 100 cells/μl increase in nadir CD4+ cell count, there was a 40% reduction in anal cancer incidence. These findings suggest that current rather than historical immunosuppression may be effective at clearing HR-HPV infection, while measures of past immunosuppression may be more predictive of anal cancer risk.

Implications of all the available evidence

This review has practical implications for the management of PLHIV and anal cancer control worldwide. Given the high prevalence of anal lesions in high-risk populations such as PLHIV and the challenges in diagnosis and effective management of anal lesions, this review points to yet one more reason to emphasize early diagnosis of HIV infection and rapid initiation and maintenance of effective ART among populations at increased risk of anal cancer.

INTRODUCTION

People living with HIV (PLHIV) are at increased risk of high-risk (HR)-HPV infection and persistence,[1] anal high-grade squamous intraepithelial lesions (HSIL+) or high-grade anal intraepithelial neoplasia (AIN2+) and incidence of anal cancer.[2, 3] Anal cancer is the fourth most common cancer among men who have sex with men (MSM) living with HIV,[4] and evidence suggests higher rates of anal cancer among women living with HIV (WLHIV) and men who have sex with women (MSW) living with HIV compared to their HIV-negative counterparts.[3, 5-7]

As antiretroviral therapy (ART) is scaled-up, longer survival times among PLHIV may be associated with an increase in the rates of anal and other cancers. A recent meta-analysis of observational studies evaluating the incidence of malignancies before and after the introduction of highly active antiretroviral therapy (HAART) reported a 4-fold increased risk in anal cancer following the introduction of HAART compared to the pre-HAART era.[8] Given the limitations in anal cancer screening,[9, 10] high rate of recurrence following management of anal lesions[11] and low access to HPV vaccination among PLHIV,[12] evidence of the impact of ART on anal HR-HPV, anal lesion and anal cancer incidence is needed.

In a previous meta-analysis, we reported that, despite wide variability in 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 cervical HR-HPV prevalence, cervical intraepithelial neoplasia (CIN) incidence or progression and invasive cervical cancer incidence.[13]

The aims of this paper 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 HR-HPV prevalence, anal intraepithelial neoplastic lesion prevalence, incidence, progression and regression, and anal cancer incidence.

METHODS

Search strategy and selection criteria

We searched Medline and Embase databases for publications in the English language using search terms for human papillomavirus (HPV), squamous intraepithelial lesions (SIL), anal intraepithelial lesions (AIN), anal cancer and antiretroviral therapy (ART, HAART) and HIV (**Appendix, page 1-4**). Reference lists of review articles and all articles identified in the systematic search were checked. The search was carried out from 1 January 1996 (when HAART became utilised) up to 30 October 2019. 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 (AC). Consensus was reached on potential relevance.

Studies were eligible if they reported, among PLHIV, the association of combination ART or HAART use (*Analysis 1*), HIV PVL (*Analysis 2*), nadir and current or contemporary (at time of outcome measure) CD4+ cell count (*Analysis 3*) with the following outcomes: anal HR-HPV prevalence, incidence and persistence; cytology- or histology-confirmed anal SIL/AIN 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 in the HAART era (i.e. from 1996 onwards), with the exception of studies reporting anal cancer incidence where follow-up of PLHIV was more commonly reported over a longer duration from the 1980s onwards. There was no restriction according to study design.

Various cut-offs for defining HIV viral detection were considered depending on assays used. To maximise the number of studies included for *Analysis 2*, we considered undetectable HIV as PVL ≤400 copies/ml. For prospective studies, the HIV-related factor of sustained viral suppression/undetectable HIV PVL over time was used (i.e. PVL <1000 copies/ml or <40 copies/ml for an established period). The majority of studies reported HIV viral detection or suppression among all enrolled participants, and not among ART users alone, although the majority of included participants were taking ART (84%). Nadir CD4+ cell count using a cut-off of 200 cells/ul and current CD4+ count using a cut-off of 500 cells/ul were used in the meta-analysis (*Analysis 3*) as these were the most frequently reported.

For HPV outcomes, studies reporting anal HR-HPV or any HPV were included. There were no exclusions on HPV test methods. For the anal lesion outcomes, studies reporting association of ART, HIV PVL and/or nadir or current CD4+ count with the incidence, progression and regression of "any AIN grade" diagnosed by histology or high-resolution anoscopy (HRA) or "any SIL grade" diagnosed by cytology, which could include atypical squamous cells of undetermined significance (ASCUS) as well as low-grade (LSIL) and high-grade (HSIL+) lesions were included, or a combination of any of the three methods (i.e. 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 relevant description of the cohort and study design and the most complete set of results was included. There was no restriction on gender, age or geographical location.

Data Extraction

From the consensus list, data were extracted by one author (HK) and a random sample of 25% was checked by a second (AC). For studies reporting prevalence of HR-HPV or anal lesions, odds ratios (OR) were extracted. For studies reporting anal lesion incidence, progression or regression, hazard ratios (HR), rate ratio (RR) or OR 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 in the post-1996 era were extracted, where available.

Methodological quality assessment

We adapted the Newcastle-Ottawa scale[15] to assess the methodological quality of studies (criteria established by HK and PM, **Appendix page 5-9**) and assessment was conducted by one author (HK). Studies were assessed on 1) representativeness of participants (i.e. proportion of ART users with undetectable HIV PVL); 2) adjustment for HIV-related factors (including any of: current and/or nadir CD4+ cell count; HIV plasma viral detection or suppression, duration on ART or years living with HIV) and history of receptive anal intercourse (RAI) and 3) ascertainment of outcome (HPV test used and method for diagnosis of SIL-AIN and anal cancer). Studies evaluating ASCUS-AIN1+ and HSIL-AIN2+ were assessed on verification method (HRA alone, cytology alone, cytology combined with HRA, histology alone or in combination), biopsy indication and proportion of participants undergoing biopsy and whether there was independent verification of final diagnosis (**Appendix, page 8-9**).

Statistical analysis

We performed meta-analyses for the discrete outcomes of HR-HPV prevalence, incidence and persistence, low-grade lesion (ASCUS-AIN1+ verified by cytology or histology), high-grade lesion (HSIL-AIN2+ by cytology or histology) prevalence, incidence, progression and regression and

incidence of anal cancer, respectively. Separate meta-analyses were conducted for the following exposures: ART use, undetectable HIV viral load or duration of undetectable HIV PVL, nadir CD4+ count (≥200 vs. <200 cells/μl) and current CD4+ count, irrespective of ART use (≥500 vs. <200 cells/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 using funnel plots and Begg's test for correlation between the effect estimate and their variances.[17, 18] Sub-group analyses by gender, sexual orientation, geographic region and study design were performed to compare pooled effects and heterogeneity. Studies that adjusted for HIV-related factors and/or RAI and were considered separately in sensitivity analyses, as were studies that scored highly on the Newcastle-Ottawa adapted scale.

We also performed meta-analysis to derive pooled prevalence of ART use, undetectable HIV PVL, reported RAI and prevalence ofHR-HPV, ASCUS-AIN1+ and HSIL-AIN2+, stratified by gender, sexual orientation and geographic region using random-effects meta-analysis.

Data were analysed using Stata version 16 (Stata Statistical Software, College Station. TX: Stata Corporation).

This review 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 review is registered on the PROSPERO database at the Centre of Reviews and Dissemination, University of York; registration number CRD42018007271. The review dataset is available on the Mendeley online repository at http://dx.doi.org/10.17632/vxbt7rc27j.1.

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RESULTS

We identified 6,777 publications through Medline and Embase searches, of which 2,022 duplicates were removed and 3,355 excluded after abstract review, leaving 1,400 articles for full text review. Finally, 118 articles matched the inclusion criteria and four additional publications[21-24] were identified through cross-referencing (**Figure 1**), representing 130 discrete populations from 122 studies providing data among 417,006 PLHIV. There were 25 (19.2%), 57 (43.8%) and 7 (5.4%) studies providing effect estimates separately for women (n=5,221), MSM (n=33,888) and MSW (including male injecting drug users [IDU]; n=1,084), respectively. Sixteen (12.3%) studies were among men only but did not provide effect estimates stratified by sexual orientation (n=82,164 men) and 25 (19.2%) studies were among a combination of women and men but did not provide effect estimates stratified by gender or sexual orientation (n=294,649 PLHIV). Two studies included both MSM and MSW (or male IDU), 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]

The majority of studies were cross-sectional and prospective cohort; the remaining studies were retrospective cohort or chart reviews, case-control or convenience, randomised control trials and

record or registry linkage studies (**Appendix, page 10**). Most studies were conducted 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%, 74.7% and 79.7% among women, MSM and MSW, respectively (**Appendix, page 11**) and undetectable HIV PVL was 71.2%, 67.0% and 62.5%, respectively. Among 40 studies, 34.6% of women and 6.8% of MSW reported ever practicing RAI. Among MSM, 60.4% reported recent (≤12 months) RAI. Among women, the pooled prevalence of anal HR-HPV, ASCUS-AIN1+ and HSIL-AIN2+ were 43.8%, 18.3% and 13.7%, respectively. These estimates were 28.6%, 23.6% and 4.1%, respectively among MSW and 69.0%, 38.0% and 30.5%, respectively among MSM .

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

In the meta-analysis of the association of ART and anal HR-HPV prevalence among 18 studies, PLHIV on ART had a 35% lower risk of anal HR-HPV prevalence compared to ART-naïve individuals (crude [c]OR=0.65, 95%CI: 0.54-0.79, adjusted [a]OR=0.45, 95%CI: 0.19-1.07, adjusted for any nadir or current CD4+ count, HIV PVL or history of RAI), with a low degree of heterogeneity between studies (I^2=24.7% for adjusted estimate, p-value for heterogeneity 0.265; **Table 2 and Figure 2**). In two studies,[30, 36] there was a 10% reduction in HR-HPV prevalence per additional year on ART (aOR=0.90, 95%CI: 0.85-0.95, I^2=0.0%, p=0.881, **Table 2**). Compared to detectable HIV PVL, undetectable HIV PVL was associated with a 33% reduction in HR-HPV prevalence (cOR=0.67, 95%CI: 0.57-0.78, I^2=4.0%, p=0.407) in 17 studies and 36% reduction in HPV16 prevalence in four studies[37-40] (cOR=0.64, 95%CI: 0.43-0.97, I^2=17.9%, p=0.301; **Appendix, page 24**).

In six studies, a high nadir CD4+ cell count was associated with lower prevalence of anal HR-HPV compared to those with low nadir CD4+ cell count among women only[22, 38, 41, 42] (≥200 versus <200 cells/μl: cOR=0.62; 95%CI: 0.43-0.90, I^2=0.0%, p=0.738; **Appendix, page 19**). Higher current CD4+ count (i.e. at time of outcome measurement) was associated with a 28% reduction in HR-HPV prevalence (≥500 versus <500 cells/μl: cOR=0.72, 95%CI: 0.60-0.87, I^2=5.1%, p=0.391) and for each 100 cells/μl current CD4+ increase, there was an 11% reduction in HR-HPV prevalence (**Table 2**) but no association was observed with HPV16 prevalence (**Appendix, page 24**).

There was no evidence to suggest publication bias for the association of any of the HIV related factors and HR-HPV prevalence (**Table 2 and Appendix, page 20**). Many studies, however, included PLHIV with poor HIV control (i.e. low proportion of ART users with detectable PVL or low median current CD4+ count) and few studies provided estimates adjusted for potential confounders (**Appendix, page 21-22**). Restricting analysis to 4 studies[23, 34, 35, 43] considered high quality (Newcastle-Ottawa score ≥5), ART use was associated with a greater reduction in HR-HPV prevalence (cOR=0.57, 95%CI: 0.38-0.86, I^2=0.0%; p=0.953; **Appendix, page 23).**

Among the studies evaluating association of HIV-related factors and ASCUS-AIN1+ prevalence, PLHIV with undetectable HIV PVL had 27% lower risk of ASCUS-AIN1+ compared to those with detectable HIV PVL (aOR=0.73, 95%CI: 0.64-0.83, I^2=0.0%, p=0.495; **Table 2** and **Figure 3**). The prevalence of ASCUS-AIN1+ was 48% lower among PLHIV with nadir CD4+ count ≥200 cells/μl and 33% lower among PLHIV current CD4+ ≥500 cells/μl.

There was a 16% reduction in HSIL-AIN2+ prevalence among PLHIV with undetectable HIV PVL cOR=0.84, 95%CI: 0.72-0.98, I^2=0.0%, p=0.800) in 16 studies, especially if sustained over long duration (≥1 year: cOR=0.62, 95%CI: 0.47-0.81, I^2=0.0%, p=0.506) in four studies (**Table 2** and **Figure 4)**.[44-47] The prevalence of HSIL-AIN2+ was also lower among PLHIV with higher nadir CD4+ count (cOR=0.60, 95%CI: 0.41-0.89, I^2=67.6%, p=0.009) but not among those with higher current CD4+ count.

For the outcomes of ASCUS-AIN1+ and HSIL-AIN2+, the main risk of bias was linked to outcome ascertainment. Most studies evaluating ASCUS-AIN1+ used cytology alone to diagnose ASCUS+ (57%); 7 (19%) conducted HRA-directed biopsy on visible lesions, 8 (22%) conducted HRA among individuals with abnormal cytology with biopsies taken from visible lesions, and one study took biopsies from individuals with both HRA-abnormal and normal findings; few studies used any independent verification of the final diagnosis (**Appendix, page 28-29**). Among two studies[32, 34] that were considered high quality (Newcastle-Ottawa score ≥5), ART was associated with a 65% reduction in ASCUS-AIN1+ prevalence (**Appendix, page 23**). Among studies evaluating HSIL-AIN2+, one (4%) used cytology alone to diagnose HSIL+; 11 (48%) conducted HRA-directed biopsy on visible lesions, 8 (35%) conducted HRA among individuals with abnormal cytology with biopsies taken from visible lesions, and three (13%) studies took biopsies from individuals with both HRA-abnormal and normal findings. The highest scoring studies (≥5 on Newcastle-Ottawa scale, n=11)[30, 44-53] included random biopsy of normal quadrants and/or an independent verification of histology (**Appendix, page 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+.

In 9 studies among 141,877 PLHIV, ART use was associated with a 34% increase in anal cancer incidence compared to 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, prior AIDS event or years living with HIV (aHR=1.11, 95%CI: 0.68-1.80, I^2=0.0%, p=0.572; **Table 3** and **Figure 5**). Two studies[54, 55] reported a 6% increased risk of anal cancer per year on ART but associations were not significant in the adjusted analysis (adjusted for pre-ART CD4+ count and HIV RNA level).[55] In two studies among 56,190 PLHIV taking ART in the USA, individuals with sustained undetectable HIV PVL (defined as percent follow-up time with undetectable HIV PVL ≥80% versus ≤20% of the time;[56] and percent follow-up time with undetectable HIV PVL ≥80% versus <40% of the time[57]) had a 44% lower risk of anal cancer incidence (aHR=0.56, 95%CI: 0.44-0.70, I^2=0.0%, p=0.938). A high nadir CD4+ cell count ≥200 cells/µl was associated with 67% lower risk of anal cancer incidence in three studies among 19,775 PLHIV.[21, 58, 59] For each 100 cells/µl increase in nadir CD4+, there was a 40% reduction in anal cancer incidence (cHR=0.60, 95%CI: 0.46-0.78, I^2=21.7%, p=0.259).[59, 60]

Most studies evaluating anal cancer were considered high quality (**Appendix, page 35**) and sensitivity analyses among the highest quality papers did not change the estimates. There was no evidence of publication bias for the studies included in the anal cancer meta-analyses.

Among studies evaluating longitudinal measures of HR-HPV and HSIL-AIN2+, there was some evidence that ART users had an 18% decreased risk of HR-HPV persistence compared to ART-naïve (**Appendix, page 24-25**) in two studies.[61, 62] There was a 61% reduction in HSIL-AIN2+ incidence among MSM taking ART compared to ART-naïve[63] and a 70% reduction among MSM with prolonged ART use (≥4 years) compared to short-term use (<4 years).[64] For each additional year on ART, there was a 7% increased likelihood of HSIL-AIN2+ clearance following lesion management.[65]

DISCUSSION

This is the first meta-analysis investigating the association of ART use, HIV plasma viral load, CD4+ cell count with the outcomes of anal HR-HPV, cytology and histology-confirmed anal squamous intraepithelial lesions and anal cancer incidence among PLHIV. The results indicate that PLHIV on ART have a lower prevalence of HR-HPV and those with undetectable HIV viral load have lower risk of high-grade lesion (HSIL-AIN2+) prevalence. Although ART was not found to be associated with anal cancer risk, ART users with sustained undetectable HIV viral load had a 44% lower risk, and a 100 cells/μl increase in nadir CD4+ count was associated with a 40% reduction in anal cancer incidence.

A binary measure of ART use may not a true measure of ART effectiveness and may dilute the positive effect of ART due to the heterogeneity in the history of immunodeficiency of ART users, as indicated by the variation in nadir CD4+ cell count. This is especially true of individuals who may have started ART in the pre- or early HAART era on older regimens or guidelines. Of the nine studies evaluating the association of ART and anal cancer, five included participants in the early HIV era (1983 onwards). A longer cumulative period of immunodeficiency or high viral replication may allow accumulation of genetic changes important for anal cancer development. It is also possible that ART-naïve participants included in these studies might have been more recently HIV-infected, with a correspondingly shorter time to experience the effect of anal HR-HPV infection and lesion development.[66] Due to this heterogeneity in past immunosuppression among ART users, some studies evaluated the association of high nadir CD4+ cell count 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 randomized controlled trials,[67-69] have demonstrated the clinical benefit of early ART initiation, including the reduction of infected-related cancers[70] and current guidelines now indicate starting ART for all PLHIV irrespective of CD4+ count[71]. Contemporary cohorts of PLHIV may consequently experience a shorter period, or none, with immunosuppression. This, coupled with sustained undetectable HIV PVL, may lead to a decrease in anal cancer incidence. However, the feasibility of universal ART access in low-and-middle income settings with respect to financing, burden on healthcare facilities, adherence and potential risk of drug resistance is uncertain.[72] Future prospective studies are needed to monitor anal cancer incidence among PLHIV globally in the era of universal and early ART.

In contrast to what was observed for anal cancer incidence, contemporary measures of ART use (irrespective of duration) and high and increasing current, but not nadir CD4+ cell count, were associated with a reduction in HR-HPV prevalence, suggesting that current rather than historical immunosuppression may be effective at clearing HR-HPV infection. Although we observed no association between ART use and HR-HPV persistence, there were too few studies reporting on this outcome. Further, prolonged ART use, accompanied with sustained undetectable HIV PVL, was associated with a decreased risk of HSIL-AIN2+ prevalence and incidence, and promoted lesion regression following management.[65]

We encountered several limitations in this review. Firstly, the majority were cross-sectional studies and many used a binary category of ART users and ART-naïve. A more informative analysis would be to measure the effect of prolonged duration of ART use and/or effective ART, as measured by viral suppression or undetectable HIV PVL, which have been shown to decrease the risk of cervical HR-HPV, cervical intraepithelial neoplasia (CIN) and cervical cancer.[13] There were also few prospective studies evaluating lesion progression and regression of anal lesions. This may be because, once detected, high grade SIL/AIN may be immediately treated. Only two studies in this review evaluated spontaneous regression.[73, 74]

Second, there was a potential for misclassification bias of anal lesion outcomes. Contrary to what was observed among studies evaluating association of ART and CIN,[13] few studies in this review had histological verification, but were based on directed biopsy indicated by cytology and/or HRA. Although there are few formal guidelines for anal cancer screening for high-risk groups including PLHIV,[75-77] cytology and HRA are frequently used to detect anal lesions but often underestimate the severity of lesions determined by the gold-standard of histology.[9, 78] While HRA is similar to cervical colposcopy, it requires extensive training and observer experience,[79] although the addition of random biopsy of normal looking quadrants has been reported to increase the number of HSIL identified when observers are less experienced.[80] Few studies had independent verification of either cytology or histology which has shown to improve accuracy of diagnosis.[81-83] As few of the included studies conducted such quality control measures, we cannot rule out the possibility of underdiagnosed high-grade disease which may contribute to the lack of associations observed. However, measures of HR-HPV infection and anal cancer incidence are less observer-dependent and associations found with these outcomes are likely to be more robust.

There is also the possibility of unmeasured confounding and few studies provided estimates adjusted for history or frequency of receptive anal intercourse. The majority of included studies were among MSM in Europe and North America and the prevalence of HR-HPV, HSIL-AIN2+ and anal cancer incidence in this group is consistent with an earlier review.[2] Conversely, there were few studies among women and MSW, and studies conducted in Africa, making it difficult to assess if trends for ART, undetectable HIV PVL and CD4+ cell count were similar by gender/sexual orientation group and geographic region. Interestingly, there was a high prevalence of anal HR-HPV reported, 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,[84] and for women via sexual transmission route. A small proportion of MSW reported ever practicing RAI, although we also cannot rule out the possibility that studies among MSW may have misreported or underreported history of RAI. Individual patient-level data meta-analysis would allow for better harmonisation of outcome and exposure definitions and adjustments which would provide a more precise and robust estimate of the association of ART and HR-HPV and anal lesion outcomes.

This review has practical implications for the management of PLHIV 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 HR-HPV and control of associated anal lesion development. Despite the large number of studies included in this review, few evaluated the impact 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 PLHIV and the challenges in diagnosis and effective management of anal lesions, this review points to yet one more reason to emphasize early diagnosis of HIV infection and immediate initiation of effective ART among populations at increased risk of anal cancer.

AUTHOR CONTRIBUTIONS

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, SS and PM contributed to the writing of the manuscript.

DECLARATION OF INTERESTS

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

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Table 1. Summary of studies included in the meta-analyses, by outcome

		All	ART vs. ART-naïve	Undetectable vs. detectable HIV PVL	Nadir CD4+ ≥200 vs. <200 cells/µl	Current CD4+ ≥500 vs. <500 cells/µl	Other[a]
All[b]	**N populations**	**130**	**79**	**68**	**29**	**40**	**27**
	N PLHIV	417006	161982	45912	26001	17390	257771
HR-HPV prevalence[22, 23, 30-32, 34-36, 38, 41-43, 85-101]	**N populations**	**29**	**18**	**17**	**6**	**8**	**4**
	N PLHIV	7750	5311	4487	1107	2505	1745
ASCUS-AIN1+ prevalence[26-28, 32-35, 102-126]	**N populations**	**37**	**28**	**20**	**10**	**11**	**2**
	N PLHIV	8790	6782	5342	1720	2198	351
HSIL-AIN2+ prevalence[30, 31, 44-53, 127-137]	**N populations**	**23**	**15**	**16**	**6**	**5**	**7**
	N PLHIV	8400	6114	6412	3056	2614	3264
Anal cancer incidence[3, 21, 54-60, 138-145]	**N populations**	**17**	**9**	**3**	**3**	**0**	**10**
	N PLHIV	380231	141877	20862	19775	..	251580
Any HPV prevalence[25, 33, 39, 40, 109, 146-152]	**N populations**	**13**	**5**	**5**	**0**	**5**	**1**
	N PLHIV	2968	559	1232	-	1098	404
HPV16 prevalence[23, 32, 37-41, 90, 96]	**N populations**	**9**	**7**	**6**	**2**	**4**	**0**
	N PLHIV	2539	1907	1848	354	1283	-
HR-HPV incidence[36, 62]	**N populations**	**2**	**2**	**0**	**0**	**0**	**0**
	N PLHIV	1345	1345	..	..	..	..
HR-HPV persistence[24, 61, 62, 153]	**N populations**	**4**	**4**	**0**	**0**	**0**	**1**
	N PLHIV	1444	1444	..	..	..	123
ASCUS-AIN1+ incidence[29, 35, 154]	**N populations**	**5**	**4**	**3**	**3**	**4**	**1**
	N PLHIV	562	514	243	243	329	233
HSIL-AIN2+ incidence[63, 64, 73, 155]	**N populations**	**5**	**1**	**2**	**0**	**3**	**2**
	N PLHIV	898	310	299	..	623	270
HSIL-AIN2+ clearance following treatment[65, 156, 157]	**N populations**	**3**	**1**	**2**	**0**	**3**	**1**
	N PLHIV	7487	120	7331	..	7487	156
HSIL-AIN2+ recurrence following treatment[158]	**N populations**	**1**	**1**	**1**	**1**	**1**	**0**
	N PLHIV	100	100	100	100	100	..
HSIL-AIN2+ spontaneous regression[73, 74]	**N populations**	**2**	**0**	**2**	**0**	**0**	**0**
	N PLHIV	261	..	261	..	..	..

[a]Category "Other" includes associations of ART duration, HIV PVL, nadir and current CD4+ count at thresholds other than that defined in this Table. All results are given in Appendix, page 24. [b]A total 122 studies were included, representing 130 populations (some studies evaluated women, MSM and MSW as discrete groups) and some studies evaluated more than one outcome; ART=antiretroviral therapy; PVL=plasma viral load; HR-HPV=high-risk papillomavirus; Any HPV=includes high risk and low risk HPV types; ASCUS-AIN1+=atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater; HSIL-AIN2+=high-grade squamous intraepithelial lesions or anal intraepithelial neoplasia, grade 2 or greater; PLHIV=people living with HIV

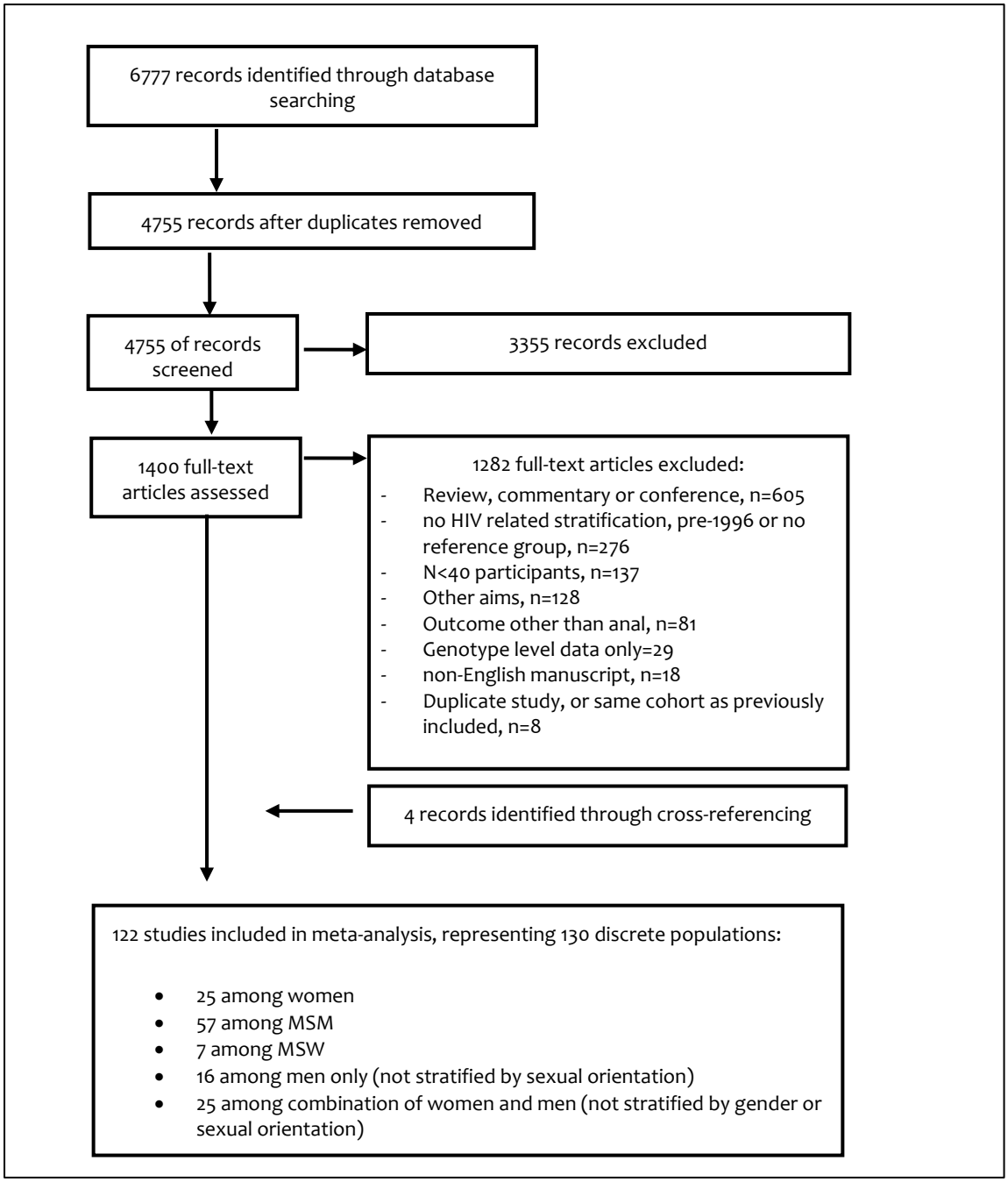
Table 2. Meta-analysis of anal HPV and related-disease outcomes according to HIV-related factors

	Crude analysis[a]					Adjusted analysis[b]				
	N studies	Effect estimate[c] (95%CI)	I^2	*P* for heterogeneity	Beggs p value[d]	N studies	Effect estimate[c] (95%CI)	I^2	*P* for heterogeneity	Beggs p value[d]
HR-HPV prevalence										
ART vs. ART naïve[22, 23, 31, 32, 34-37, 41, 43, 85, 87, 90, 91, 93, 95, 96, 101]	18	0.65 (0.54-0.79)	12.1%	0.310	0.622	3	0.45 (0.19-1.07)	24.7%	0.265	..
Per year on ART[30, 36]	..	..	..	..	..	2	0.90 (0.85-0.95)	0.0%	0.881	..
Undetectable vs. detectable HIV PVL[22, 30, 31, 36, 38, 42, 43, 86, 88, 89, 94-98, 101]	17	0.67 (0.57-0.78)	4.0%	0.407	0.621	2	0.75 (0.52-1.09)	0.0%	0.412	..
Nadir CD4+ ≥200 vs. <200 cells/µl[22, 38, 41, 42, 98, 101]	6	0.68 (0.40-1.14)	58.9%	0.033	..	1	0.27 (0.08-0.95)	..	..	..
Nadir CD4+ per 100 cells/µl increase[30, 35]	2	1.02 (0.76-1.36)	73.1%	0.054	..	..	..	..	..	..
Current CD4+ ≥500 vs. <500 cells/µl[23, 38, 43, 87, 89, 92, 97, 100]	8	0.72 (0.60-0.87)	5.1%	0.391	..	..	..	..	..	..
Current CD4+ per 100 cells/µl increase[30, 35]	..	..	..	..	..	2	0.89 (0.81-0.97)	0.0%	0.579	..
ASCUS-AIN1+ prevalence										
ART vs. ART naïve[26, 27, 32-35, 102-104, 107-112, 116-122, 124-126]	28	0.96 (0.74-1.25)	55.4%	<0.001	0.782	2	0.52 (0.08-3.47)	79.4%	0.03	..
Undetectable vs. detectable HIV PVL[26, 27, 32, 33, 102, 103, 105-108, 111, 117, 120-122, 124, 125]	20	0.73 (0.64-0.83)	0.0%	0.495	0.011	1	0.70 (0.57-0.86)	..	..	..
Nadir CD4+ ≥200 vs. <200 cells/µl[27, 102, 105, 106, 108, 111, 124, 125]	10	0.52 (0.40-0.67)	0.0%	0.534	0.325	..	..	..	..	..
Current CD4+ ≥500 vs. <500 cells/µl[28, 105, 113-115, 118, 121, 123, 126]	11	0.67 (0.48-0.91)	43.4%	0.061	0.815	1	0.59 (0.37-0.92)	..	..	..
Current CD4+ per 100 cells/µl increase[35, 116]	2	0.92 (0.80-1.07)	0.0%	0.892	..	1	0.91 (0.68-1.14)	..	..	..
HSIL-AIN2+ prevalence										
ART vs. ART naïve[31, 44-50, 52, 53, 128, 131, 133, 134, 136]	15	1.18 (0.81-1.73)	48.0%	0.020	0.347	4	1.95 (0.80-4.77)	63.8%	0.04	..
Undetectable vs. detectable HIV PVL[30, 31, 44-47, 49, 50, 52, 53, 127, 128, 130, 132-134]	16	0.84 (0.72-0.98)	0.0%	0.800	0.528	..	..	..	..	..
Sustained undetectable HIV PVL[e] [44-47]	4	0.62 (0.47-0.81)	0.0%	0.506	„	1	0.61 (0.42-0.88)	..	..	..
Nadir CD4+ ≥200 vs. <200 cells/µl[44, 45, 47, 52, 53, 137]	6	0.60 (0.41-0.89)	67.6%	0.009	..	1	0.29 (0.12-0.67)	..	..	..
Nadir CD4+ per 100 cells/µl increase[30, 47]	2	0.99 (0.92-1.08)	0.0%	0.642	..	1	1.00 (0.92-1.09)	..	..	..

	Crude analysis[a]					Adjusted analysis[b]				
	N studies	**Effect estimate[c] (95%CI)**	**I^2**	***P* for heterogeneity**	**Beggs p value[d]**	**N studies**	**Effect estimate[c] (95%CI)**	**I^2**	***P* for heterogeneity**	**Beggs p value[d]**
Current CD4+ ≥500 vs. <500 cells/µl[31, 47, 51, 52, 133, 135]	5	0.72 (0.46-1.13)	79.2%	0.001	..	..	..	..	..	..
Current CD4+ per 100 cells/µl increase[30, 129, 134]	3	0.90 (0.78-1.04)	52.2%	0.123	..	2	0.97 (0.85-1.12)	5.0%	0.305	..
Anal cancer incidence										
ART vs. ART naïve[21, 55, 58, 60, 138, 140, 141, 143, 144]	9	1.34 (0.99-1.81)	0.0%	0.876	..	3	1.11 (0.68-1.80)	0.0%	0.572	..
Per year on ART[54, 55]	2	1.06 (1.01-1.11)	0.0%	0.798	..	1	1.04 (0.91-1.20)	..	..	..
Undetectable vs. detectable HIV PVL[f(139-141)]	3	0.84 (0.56-1.27)	0.0%	0.587	..	2	0.90 (0.57-1.42)	0.0%	0.442	-
Sustained undetectable HIV PVL[e (56, 57)]	..	..	..	..	..	2	0.56 (0.44-0.70)	0.0%	0.938	..
Nadir CD4+ ≥200 vs. <200 cells/µl[21, 58, 59]	3	0.33 (0.18-0.60)	0.0%	0.794	..	2	0.34 (0.16-0.71)	0.0%	0.507	..
Nadir CD4+ per 100 cells/µl increase[59, 60]	2	0.60 (0.46-0.78)	21.7%	0.259	..	1	0.65 (0.50-0.85)	..	..	..
Current CD4+ per 100 cells/µl increase[3]	..	..	..	..	..	1	0.89 (0.71-1.10)	..	..	..

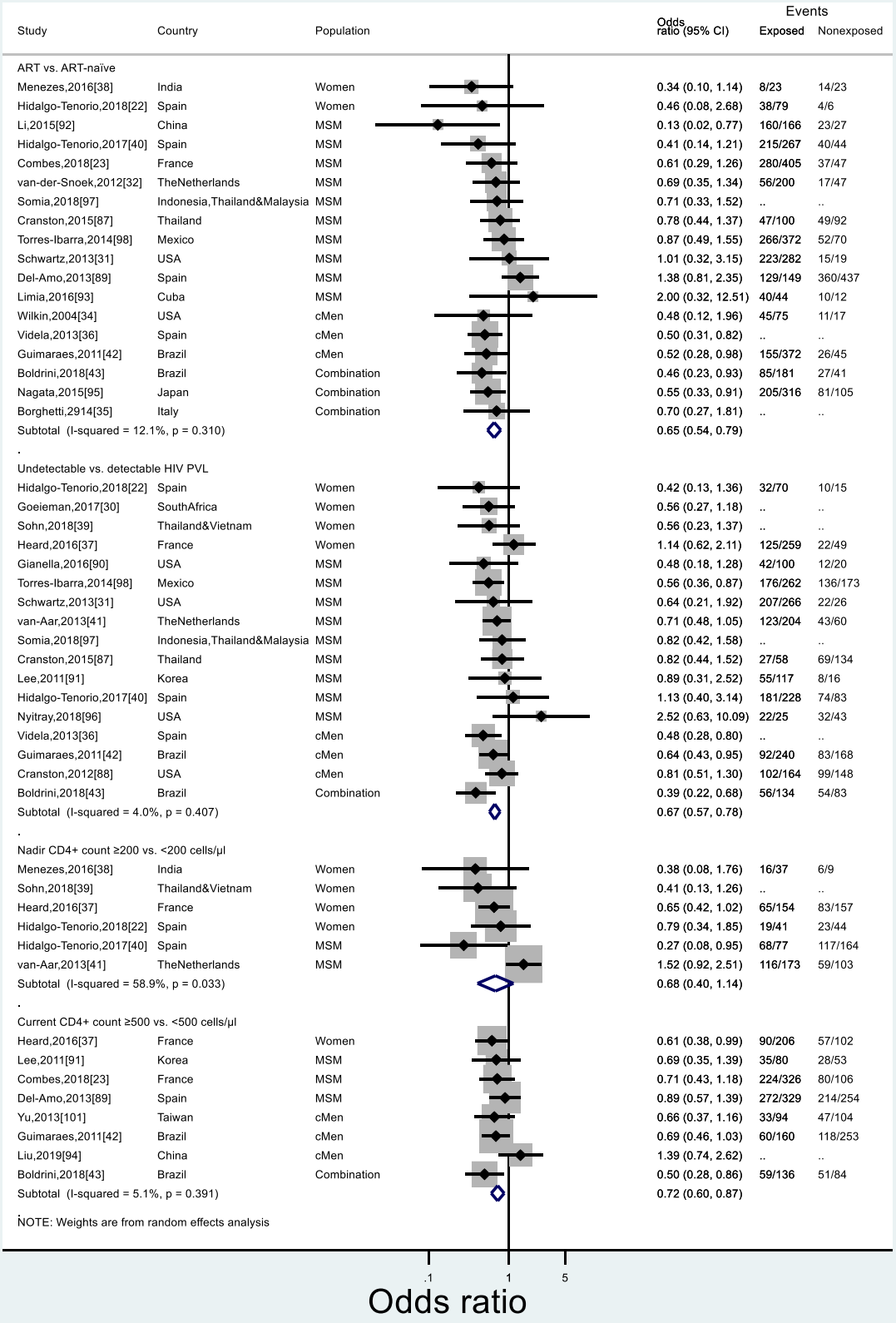
[a]includes studies with either 1.) no adjustment and 2.) studies that adjust for sociodemographic factors only but no adjustment for HIV-related factors or history of receptive anal intercourse (RAI); [b]adjusted for at least one of the following: time on ART, HIV PVL, current CD4+ cell count; nadir CD4+ cell count, years living with HIV, receptive anal intercourse (RAI); [c]Odds Ratio (OR) used for prevalent outcomes, Hazard Ratio (HR) or Rate Ratio (RR) used for prospective outcomes; [d]Begg's test is used for identifying publication bias in a meta-analysis, publication bias is considered when p-value <0.05; Beggs p-value not reported when number of studies included in meta-analysis is fewer than 10; [e]For outcome of HSIL-AIN2+ prevalence: sustained undetectable HIV PVL viral defined as: undetectable HIV PVL <50 copies/ml for >2 years compared to detectable HIV or undetectable HIV of shorter duration[44]; 1-5 years versus. <1 year living with viral suppression (defined as having a viral load of less than 200 in tests from 1 August 1999 onwards allowing for a onetime blip in viral load between 200 and 400 copies/ml)[47] , undetectable HIV PVL versus. detectable for previous 2 years[45] and viral suppression for ≥3 years compared to <3 years [46]; for outcome of anal cancer incidence, sustained HIV viral detection or suppression defined as percent undetectable HIV PVL ≥80% versus ≤20% of the time among ART users[56] and undetectable HIV PVL ≥80% versus <40% of the time among ART users[57]; note: it cannot be ruled out the possibility that both these analyses are conducted among the same individuals (data from the US Veterans Administration HIV Clinical Case Registry but published seperately) [f]a cut-off of <400 copies/ml used by[140], <500 copies/ml by [139] and <1000 copies/ml by[141].

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

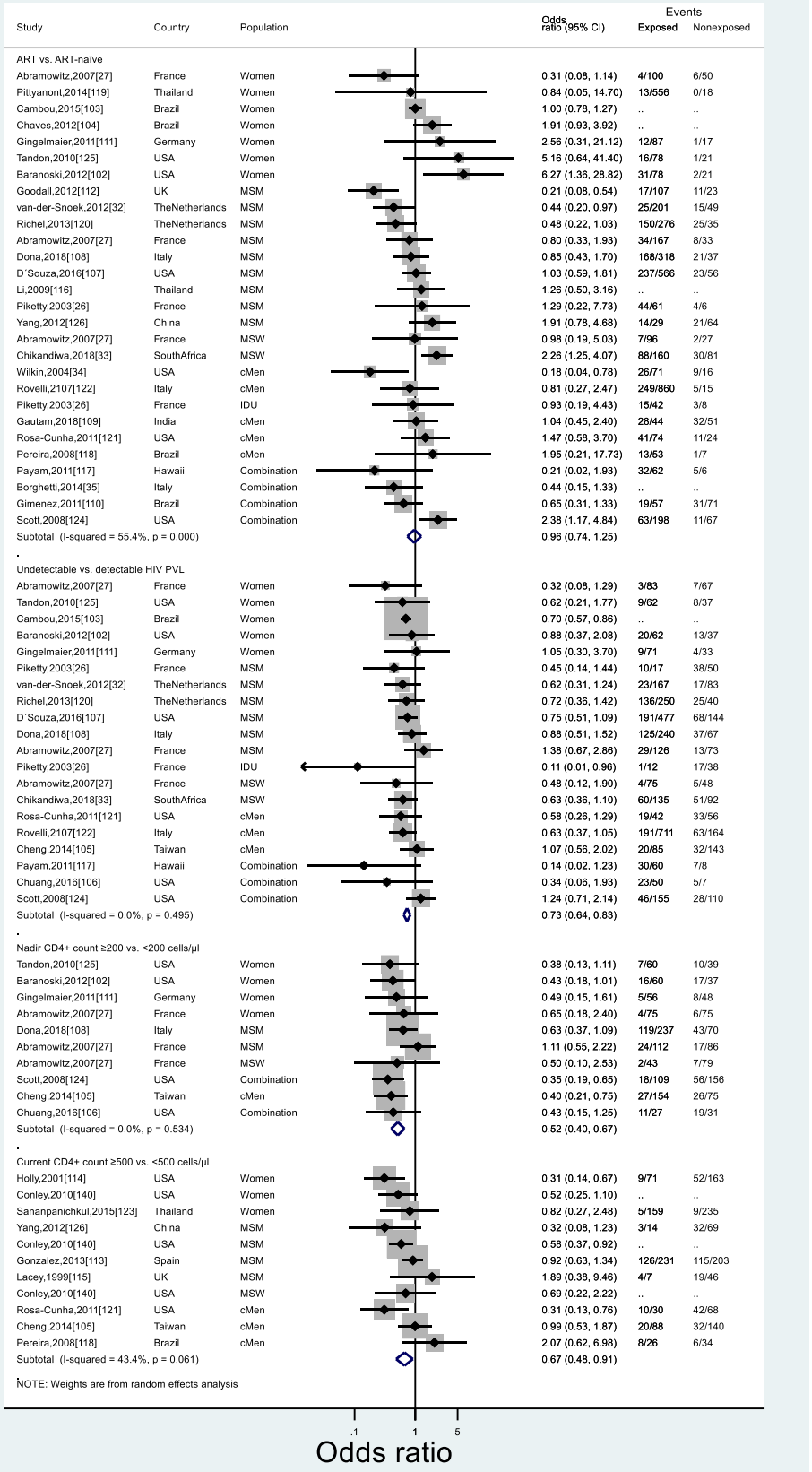
Figure 2. Meta-analysis of HIV-related factors and anal HR-HPV



For the analysis of ART vs. ART-naïve, the exposed group included ART users and non-exposed included ART-naïve individuals; for the analysis of undetectable vs. detectable HIV PVL, the exposed group included individuals with undetectable HIV PVL and non-exposed included individuals with detectable HIV PVL (irrespective of ART use); for the analysis of sustained HIV viral suppression, the exposed group includes individuals with sustained viral suppression and non-exposed included individuals without sustained viral suppression, as defined in footnote of Table 2; for the analysis of nadir CD4+ ≥200 vs. <200 cells/µl, the exposed group includes individuals with nadir CD4+ ≥200 and non-exposed included individuals with nadir CD4+ <200; for the analysis of current CD4+ ≥500 vs. <500 cells/µl, the exposed group includes individuals with current CD4+ ≥500 and non-exposed included individuals with current CD4+ <500; One study[42] compared nadir CD4+ ≥500 to nadir CD4+ <200 cells/µl; one study[32] uses data for outcome of HR-HPV only (i.e. no co-infection with non-HR types); one study[35] compares individuals taking PI/r-based

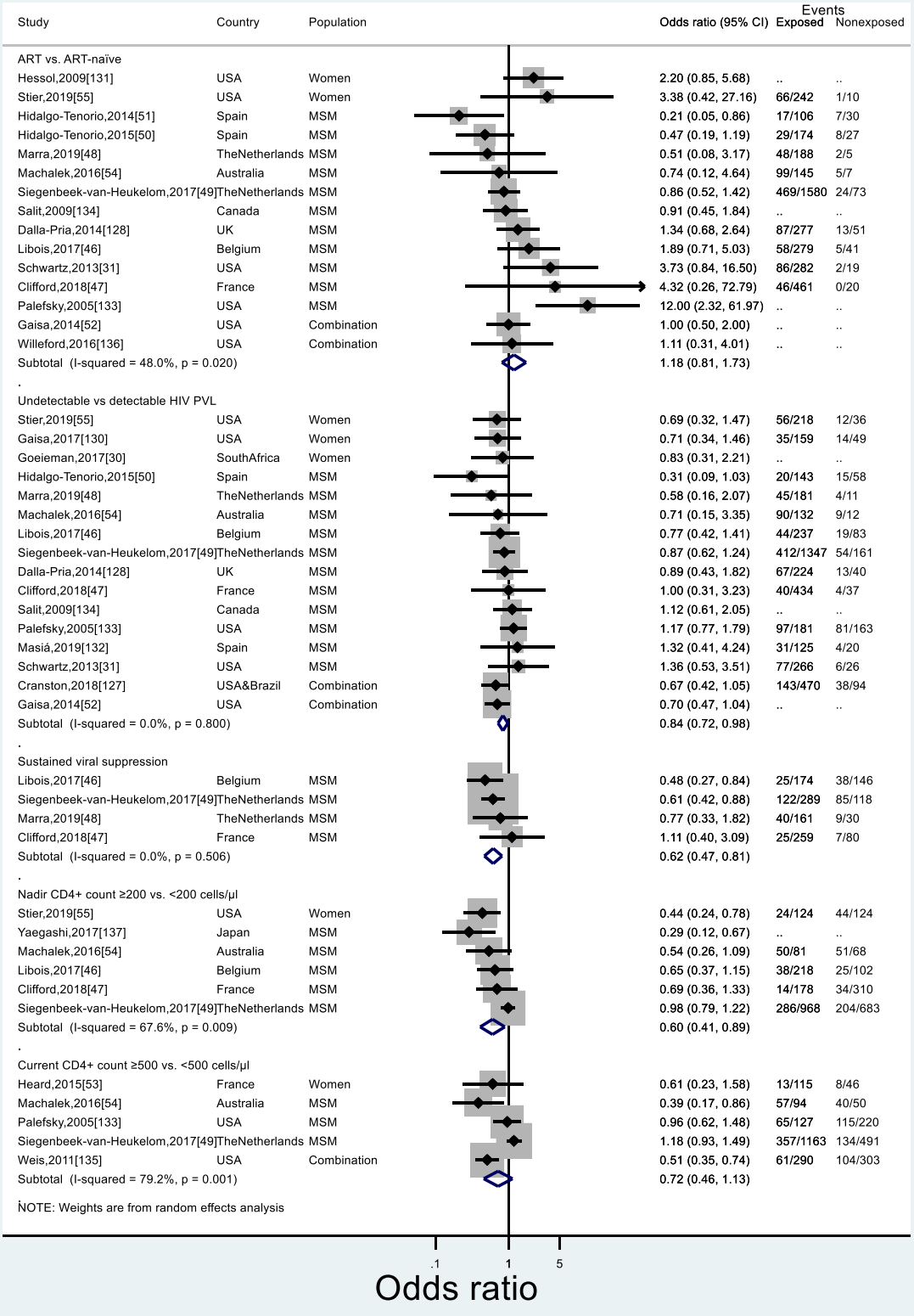
regimen vs. ART-naïve; cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation; Combination= combination of women and men for whom sexual orientation is not defined or effect estimate not given according to gender or sexual orientation; 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



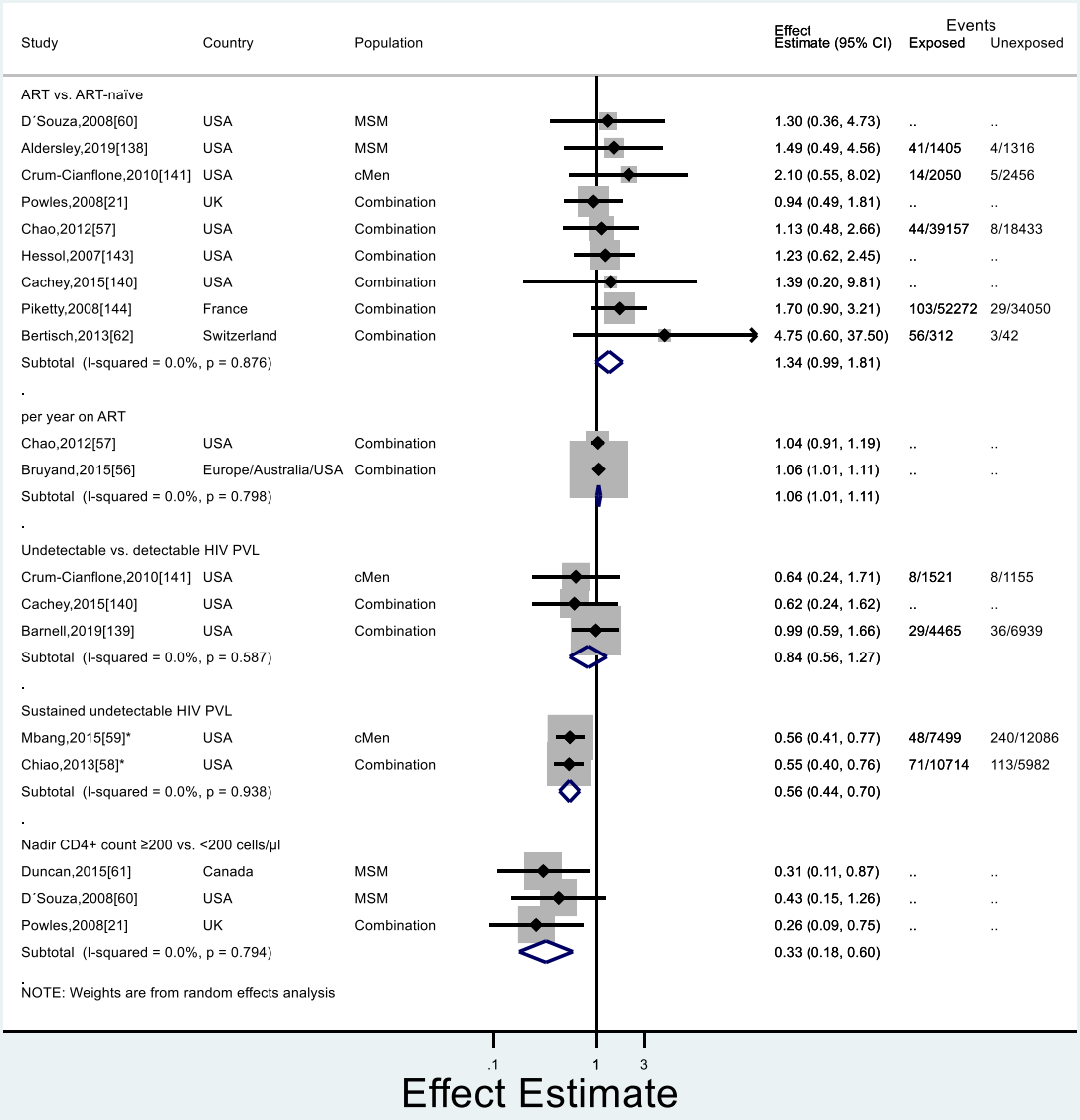
cMen=combination of men for whom sexual orientation is not defined or effect estimate not given according to sexual orientation; Combination= combination of women and men for whom sexual orientation is not defined or effect estimate not given according to gender or sexual orientation; IDU=injecting drug users; ASCUS-AIN1+=atypical squamous cells of undetermined significance or anal intraepithelial neoplasia, grade 1 or greater; 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+, one study[135] reports the association of current CD4+ ≥400 vs. <400 cells/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 gender 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



In the exposed and unexposed groups, the number of individuals is used as denominator for all studies except one study[55] for which person years (per 100,000 person-years) is used as denominator; * sustained HIV viral detection or suppression defined as percent undetectable HIV PVL ≥80% versus ≤20% of the time among ART users[56] and undetectable HIV PVL ≥80% versus <40% of the time among ART users[57]; note: it cannot be ruled out the possibility that both these analyses are conducted among the same individuals (data from the US Veterans Administration HIV Clinical Case Registry but published separately); the estimate used for [58] is restricted to period 1996-2007; the estimate for [144] is restricted to period 1998-2004; 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; MSM=men who have sex with men; MSW=men who have sex with women; PVL=plasma viral load.

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