Antiretroviral therapy and detection of high-grade cervical intraepithelial neoplasia (CIN2+) at post-CIN management follow-up among women living with HIV: a systematic review and meta-analysis

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Summary

We evaluated the association of ART on CIN2+ detection at follow-up among women living with HIV and found that ART was associated with a decreased risk of CIN2+ detection at follow-up particularly in high-income countries and following excisional CIN management.

Abstract

Background: We evaluated the association of antiretroviral therapy (ART), CD4+ count and HIV plasma viral load (PVL) on high-grade cervical intraepithelial neoplasia (CIN2+) detection at follow-up after CIN management among women living with HIV (WLHIV).

Methods: Medline, Embase, Global Health and PubMed were searched from January 1, 1996 to January 15, 2020. Eligible studies investigated the association of ART, CD4+ count or HIV PVL on histology-confirmed CIN2+ detection at follow-up. Summary estimates were obtained using random-effects meta-analyses; heterogeneity was examined using I^2 statistic. PROSPERO registration:CRD42018115631.

Results: Eight studies representing 9 populations were identified, including 1,452 WLHIV followed between 6 to 33 months post-CIN management. Pooled data from 8 populations (n=1,408) suggested weak evidence of a decreased risk of CIN2+ detection at follow-up among ART users compared to ART-naïve women (crude odds ratio [cOR]=0.70, 95% CI: 0.36-1.36; I^2=64.5%, p=0.006; adjusted risk ratio [aRR] from 3 studies=0.66, 95%CI: 0.20-2.24; I^2=78.7%, p=0.009). A significant association was observed in high-income countries (cOR=0.24, 95%CI: 0.13-0.45; I^2=0.0%, p=0.77) but not in low and middle-income countries (cOR=1.13, 95%CI: 0.67-1.92; I^2=18.8%, p=0.30).

In three populations, ART users with HIV PVL <50 copies/ml were less likely to have CIN2+ detection at follow-up (vs. ≥50 copies/ml: cOR=0.55, 95%CI: 0.32-0.94; I^2=0.0%, p=0.23).

There was weak evidence of decreased CIN2+ detection at follow-up among WLHIV with higher contemporary CD4+ cell counts (≥200 cells/μl vs. <200 cells/μl [cOR=0.36, 95%CI: 0.04-3.13; I^2=81.3%, p=0.021]) and significant evidence among women with a higher nadir CD4+ count (≥350 cells/μl vs. <200 cells/μl [adjusted hazard ratio [aHR]=0.35, 95%CI: 0.15-0.84; I^2=0%, p=0.64]).

Conclusion: ART may reduce the risk of CIN2+ detection at follow-up; this effect is most likely enhanced by a combination of adequate HIV control and excisional CIN treatment. Our findings support recommendations of early ART and the integration of CIN2+ screening and management into HIV care.

Keywords: Cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL), cervical cancer, HIV infections, antiretroviral therapy (ART), plasma viral load (PVL), CD4+ cell count

This review is registered on the PROSPERO database at the Centre of Reviews and Dissemination, University of York; registration number CRD42018115631

Introduction

Invasive cervical cancer (ICC) is the fourth most common cancer and the fourth leading cause of cancer death in women [1]. In 2018, there were 311,365 deaths from ICC worldwide, with the vast majority occurring in low and middle-income countries (LMICs)[1].

The predominance of ICC in LMICs is exacerbated by poor coverage of ICC screening[2], a low availability of human papillomavirus (HPV) national vaccine programs[3,4] and a concurrent high burden of HIV[5].

Compared to HIV-negative women, women living with HIV (WLHIV) are more likely to acquire HPV and less likely to clear infection[6], and consequently, have a higher incidence of high-grade cervical intraepithelial neoplasia (CIN)[7,8] and ICC[9]. Moreover, WLHIV also experience poorer CIN management outcomes, being 3 times more likely to be detected with CIN at follow-up compared to HIV-negative women[10].

A previous meta-analysis showed effective antiretroviral therapy (ART) to be associated with a decreased risk of high-risk (HR)-HPV prevalence, CIN incidence and progression, and ICC incidence[11]. It did not evaluate the association of ART and CIN detection at follow-up following CIN management among WLHIV. Given the improved life expectancy of WLHIV following the scale-up of ART worldwide, an in-depth understanding of the factors driving poor CIN management outcomes among WLHIV is important for optimal patient management and follow-up.

Previous reviews have aimed to identify the histopathological predictors of CIN detection at follow-up of CIN management[10,12–14]. However, none have yet evaluated HIV-related predictors among WLHIV. We aimed to systematically review the literature on the association of ART, HIV plasma viral load (PVL), CD4+ cell counts and CIN detection at follow-up of CIN management among WLHIV.

Methods

Medline, Embase, Global Health and PubMed electronic databases were searched from Jan 1, 1996 (when highly active ART [HAART] became utilised) to January 15, 2020 (**Appendix A**). authors (N.A. and H.K.) independently assessed the eligibility of each paper. Disagreements were resolved by consensus.

Eligible studies included WLHIV who were managed for CIN, had at least one follow-up visit to estimate risk of histology-confirmed high grade CIN (CIN2+) at follow-up and evaluated the association of CIN2+ detection at follow-up with at least one of the following: ART (at the time of CIN management), HIV PVL (measured at or within 12 months of CIN management), CD4+ cell count at time of CIN management (baseline), at time of follow-up (contemporary) or nadir CD4+ (lowest CD4+ cell count ever recorded). Studies which had CIN1 as outcome and/or used only cytology at follow-up of CIN management were excluded.

In this review, we use the term 'detection at follow-up' to incorporate the different outcomes reported by the authors (**Table 1**), as it is difficult to distinguish between recurrent lesions, new lesions and persistent lesions (treatment failure) at follow-up of CIN management.

Quality assessment

The Critical Appraisal Skills Program (CASP) tool for cohorts[15] was used to assess methodological quality **(Appendix B).** Studies that enrolled women prior to treatment without histological confirmation were considered at risk of misclassification bias, due to the low specificity of non-histological diagnostic methods[16]. Studies which included participants with a history of failed CIN treatment prior to enrolment were considered at risk of bias because these participants may have been at increased risk of poor management outcomes.

We considered both HIV-related confounders (ART use, ART duration, CD4+ cell counts (baseline, contemporary and nadir), HIV plasma viral load) and non-HIV related confounders. Low-risk studies adjusted for any HIV-related confounders; medium-risk did some non-HIV related adjustment while high risk studies had no adjustments done (**Appendix B).**

Statistical analysis

The form for data extraction was adapted from published guidelines[17] and included effect estimates (odds ratios [OR], risk ratios [RR] and hazard ratios [HR]), raw data to calculate odds ratios and information to allow for description of study characteristics.

Adjusted effect estimates were reported where available. For studies in which adjusted estimates were not reported but raw data were provided, crude OR were calculated.

CIN2+ detection at follow-up was compared between WLHIV on ART and ART-naïve WLHIV (**Analysis 1**); between WLHIV with undetectable HIV PVL (<50 copies/ml) and WLHIV with detectable HIV PVL (≥50 copies/ml) (**Analysis 2**). Further analyses compared CIN2+ detection at follow-up among WLHIV according to: baseline CD4+ count (≥500 cells/μl vs. <500 cells/μl), contemporary CD4+ count (≥200 cells/μl vs. <200 cells/μl and ≥500 cells/μl vs. <500 cells/μl) and nadir CD4+ counts (≥350 cells/μl vs. <200 cells/μl) (**Analysis 3**). The cut-off values for CD4+ counts were chosen to reflect those reported in the included studies.

Data were pooled using a random-effect meta-analysis that accounts for between-study heterogeneity[18]. Several subgroup analyses were carried out according to: country income level (high/upper-middle income [HMIC] and low/lower middle-income [LMIC], using World Bank classification[19]); type of CIN management (excision [loop electrical excision therapy and conization] and ablation [cryotherapy, thermo-coagulation and laser ablation]) and interval between CIN management and CIN2+ detection at follow-up (≤12 months and >12 months). Data were analysed using Stata version 14.

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[20] and is registered on the PROSPERO database at the Centre of Reviews and Dissemination, University of York; registration number CRD42018115631. The review dataset is available on the Mendeley online repository (doi: 10.17632/3wb4nxbrhn.2).

Results

Four hundred and four records were identified, of which 128 duplicates were removed, and 230 records were excluded after title/abstract review, leaving 43 articles for full-text review (**Figure 1**). Of these, 8 articles[21–28], representing 9 discrete populations and 1,452 women, met the inclusion criteria. One study[24] provided separate effect estimates for two populations: WLHIV who received cryotherapy and WLHIV who received excisional therapy.

The characteristics of the included studies are summarised in **Table 1.** The WLHIV had a median follow-up duration ranging between 6 and 33 months. The proportion of ART users ranged between 65% and 92%; between 53% and 65% of WLHIV had HIV PVL <50 copies/ml and median CD4+ cell counts ranged from 322 cells/µl to 557 cells/µl. Of the three populations that studied the association of ART and CIN2+ detection at follow-up in HMICs[22,25,28], excisional management methods were used in one[28] and a combination of excision and ablative methods were used in two, although most women were treated using excisional methods (77% and 85%)[22,25]. Of the five populations evaluated in LMICs, excision and ablative methods were used in two[24,26] and three[23,24,27] populations respectively **(Table 1**).

For most studies, the main limitations in study quality were due to insufficient adjustment of HIV-related confounders and risk of attrition bias **(Appendix B)**. Also, although we excluded studies without histopathological confirmation of CIN2+ at follow-up, there was still risk of misclassification as some included studies had a biopsy indication following cytology. There could have been an underestimation of true detection at follow-up if some women were excluded from biopsy on the basis of follow-up cytology results.

Association of ART and CIN2+ detection at follow-up (Analysis 1)

Seven studies, representing 8 populations and 1, 408 women assessed the association of ART use and CIN2+ detection at follow-up[22–28] There was weak evidence of a decrease in CIN2+ detection at follow-up among ART users compared to ART-naïve women (crude OR [cOR]=0.70, 95% confidence interval [CI]: 0.36-1.36; I^2=64.5%, p=0.006; **Figure 2**). Three studies[25–27] provided adjusted values and when pooled together did not significantly

modify the estimate (cRR=0.66, 95%CI: 0.20-2.24; I^2=78.7%, p=0.009; adjusted for age, CD4+ cell count and WHO clinical stage; data not shown). Excluding two populations[23,26] in which 10.6% and 9% of ART users initiated ART after CIN treatment provided statistically significant evidence (cOR=0.50, 95% CI: 0.27-0.94; I^2=55.8%, p=0.045; data not shown).

There was a significantly decreased risk in CIN2+ detection at follow-up among ART users in studies conducted in high and upper middle-income countries (HMICs)[22,25,28] (cOR=0.24, 95%CI: 0.13-0.45; I^2=0.0%, p=0.77; **Table 2, Appendix C**) but not in low and lower middle-income countries (LMICs)[23,24,26,27] (cOR=1.13, 95%CI: 0.67-1.92; I^2=18.8%, p=0.30; **Table 2, Appendix C**).

In 5 populations[22,24–26,28] that used excisional methods for CIN management, there was some evidence of a decreased risk of CIN2+ detection at follow-up among ART users compared to ART-naïve WLHIV (cOR=0.53, 95%CI: 0.19-1.52; I^2=70.4%, p=0.009) but not in 3 populations[23,24,27] using ablative methods (cOR=0.92, 95%CI: 0.52-1.65; I^2=19.1%, p=0.29; **Table 2, Appendix D**).

Restricting the meta-analysis to 4 populations[24,25,28] with >12 months interval between CIN management and follow-up, there was weak evidence of a decreased risk in CIN2+ detection at follow-up among ART users compared to ART-naïve women (cOR=0.51, 95%CI: 0.17-1.52; I^2=65.7%, p=0.033; **Table 2)** but not among studies with a ≤12 months interval[22,23,26,27], (cOR=0.94, 95%CI: 0.36-2.45; I^2=71%, p=0.02; **Table 2, Appendix E**).

There was no evidence to suggest publication bias for the association of ART and CIN2+ detection at follow-up (p=0.266 and p=0.179 for Begg's rank correlation test and Egger's weighted regression, respectively; **Appendix F**).

Association of HIV plasma viral load and CIN2+ detection at follow-up (Analysis 2)

In two studies[22,24] representing three populations and 540 WLHIV, there was significant evidence that ART users with undetectable HIV PVL (<50 copies/ml) had a decreased risk of CIN2+ detection at follow-up compared to WLHIV on ART with detectable (≥50 copies/ml) HIV PVL (cOR=0.55, 95%CI: 0.32-0.94; I^2=32.4%; p=0.23; **Figure 2**)

In another study[21] (n=44), not included in the meta-analysis due to different cut-offs, crude estimates suggested no difference in CIN2+ detection at follow-up between WLHIV

with HIV PVL >10,000copies/ml compared to WLHIV with HIV PVL<1,000 copies/ml (cOR=1.5, 95%CI: 0.33-6.80; **data not shown**).

Association of baseline, contemporary and nadir CD4+ cell counts and CIN2+ detection at follow-up (Analysis 3)

Seven studies[21–24,26–28], representing 8 study populations and 1,331 WLHIV, assessed CD4+ cell count as a possible predictor of CIN2+ detection at follow-up and were included in the various sub-analyses (**Figure 3; Table 2**).

In 2 studies representing 3 populations[23,24], women with high CD4+ count at the time of CIN management (baseline CD4+) had a non-significant increased risk of CIN2+ detection at follow-up (≥500 vs. <500 cells/µl: cOR=1.48, 95%CI: 0.93-2.34; I^2=0%, p=0.51; **Figure 3, Table 2).**

When considering CD4+ count at time of follow-up (contemporary CD4+), women with higher contemporary CD4+ cell count had a non-significant decreased risk of CIN2+ detection at follow-up compared to women with lower CD4+ cell count (≥200 vs. <200 cells/µl: cOR=0.36, 95%CI: 0.04-3.13; I^2=81.3%, p=0.02; ≥500 vs. <500 cells/µl: cOR=0.71, 95%CI: 0.29-1.74; I^2=22.1%, p=0.28; **Figure 3, Table 2)**.

In two studies[22,26], nadir CD4+ count ≥350 cells/µl [22,26] was associated with a 65% decreased risk of CIN2+ detection at follow-up compared to nadir CD4+ <200 cells/µl (aHR=0.35, 95%CI: 0.15-0.84; I^2=0%, p=0.64; adjusted for age and region; **Figure 3 and Table 2**).

Discussion

In this meta-analysis, ART was associated with a reduced risk of CIN2+ detection at follow-up, particularly among ART users in HMICs. Also, a significantly lower risk of CIN2+ detection at follow-up was found among WLHIV with undetectable HIV PVL and WLHIV with high nadir CD4+ cell counts.

The difference in the effect of ART according to country income category may be attributable to different factors. First, compared to WLHIV in LMICs, WLHIV in HMICs are more likely to be on effective ART (i.e. have undetectable HIV PVL) possibly due to better access and adherence to ART, a higher likelihood of initiating ART earlier at higher CD4+ cell counts and a greater probability of retention in care[29]. Second, women in HMICs are more likely to undergo excisional management which has been shown to be more effective than ablative CIN management among WLHIV[24,30] and, as shown in our results, ART is perhaps more likely to be beneficial following excisional management. The link between adequate HIV control and improved CIN management outcomes was supported by the lower risk of CIN2+ detection at follow-up among WLHIV with undetectable HIV PVL and among WLHIV with higher CD4+ cell counts. Furthermore, the significant benefit of ART which was observed after exclusion of studies where about 10% of ART users initiated ART after CIN management, though possibly due to chance, could also point to the significance of the timing of ART use in improving CIN management outcomes. A large cohort of South African women (n=778), found a 30% decreased risk of CIN1+ detection at follow-up among WLHIV who initiated ART prior to CIN management compared to WLHIV who initiated ART after CIN management[31].

The finding that ART reduced the risk of CIN2+ detection at follow-up after excisional but not after ablative CIN management contrasts the findings of a recent meta-analysis indicating no difference in the prevalence of high-grade lesions at follow-up among WLHIV that underwent excisional versus ablative methods. However, there was no direct comparison between both treatment methods and the inclusion of cytology at follow-up could have introduced bias[32]. In support of a superior effect of excisional therapy, it may be postulated that, given the multiple immune evasion mechanisms employed by HR-HPV[33,34] it is harder for immunosuppressed WLHIV to mount an effective HPV-specific cellular immune response and methods that physically remove as much of the lesion

(such as excision which cuts 15mm deep whilst ablation cuts 7-8mm deep[35]) stand a better chance of eradicating the HPV virus. This is supported by a recent meta-analysis where WLHIV with positive margins had 3 times the odds of failing treatment compared to WLHIV with negative margins[32].

ART was associated with some improvement in outcome among studies which followed women over 12 months but not among studies with a shorter follow-up duration (≤12 months). In the studies included in this review, lesions may have continued to occur even after the end of the studies, particularly in studies with a shorter duration of follow-up. In fact, findings from a 15-year long cohort study among 37,142 women in Canada suggested a cut-off of 6 years follow-up to detect the largest number of post-management CIN lesions[36].

WLHIV on ART with undetectable HIV PVL had a significantly lower risk of CIN2+ detection at follow-up compared to WLHIV on ART with detectable HIV PVL. However, based on data from the included studies, it is not clear whether WLHIV with viral suppression (at WHO recommended cut-off of 1000 copies/ml, which is widely used for clinical management of HIV disease and a routinely monitored indicator) fare better than women with no suppression (ineffective ART). One study found no difference in the risk of CIN1+ detection at follow-up between WLHIV with 'virological failure and WLHIV with 'no virological failure', although the definition of 'virological failure' was unclear and, given the time-dependent nature of HIV PVL, there was potential misclassification, as the time relationship between the measurement of HIV PVL and CIN management or follow-up was not considered[31]. Furthermore, CIN1 is not an adequate endpoint to measure risk of cervical cancer.

The association between lower CD4+ cell counts and an increased risk of CIN detection at follow-up, though non-significant, was consistent across most CD4+ cell count cut-offs considered. This is biologically plausible because CD4+ cells are essential for the immune control of HR-HPV infection[33]. Strangely, there was some evidence suggesting a higher risk of CIN2+ detection at follow-up with baseline CD4+ ≥500 cells/μl. We think this was possibly confounded as they were all crude estimates and the finding diverged from those of other CD4+ categories and biological plausibility. Furthermore, a nadir CD4+ cell

count >350 cells/μl was associated with a decreased risk of CIN2+ detection at follow-up. This could reflect baseline CD4+ cell count which was not accounted for and, one study found no effect of nadir CD4+ cell count on CIN2+ detection at follow-up after adjusting for baseline CD4+ cell count[22]. However, it also supports the suggestion of a CD4+ nadir threshold below which subsequent ART-induced immune reconstitution does not optimally protect against serious non-AIDS events such as CIN[37]. Therefore, although nadir CD4+ cell count is a known strong predictor of CIN2+ incidence and progression[38], it could also be an important risk factor for poor CIN management outcomes.

Taken all together, it is reasonable to say that ART may reduce the risk of CIN2+ detection at follow-up but this association is likely influenced by a combination of adequate HIV control (recovery of cellular immunity and suppression of HIV PVL) and excisional CIN treatment, factors which are less likely in LMICs where the burden of HIV and invasive cervical cancer is highest.

There are some limitations to this study.

Although studies reporting on CIN1 at follow-up were excluded (as CIN1 is has recently been considered a manifestation of acute HPV infection and not a true precursor lesion of cervical cancer[39]), CIN2 is still subject to misclassification as its diagnosis has poor replicability and a high proportion regress spontaneously[40]. Therefore, as no studies reported solely on CIN3, the real precursor lesion of cervical cancer[41], residual misclassification of precancerous lesions cannot be ruled out.

The few number of studies that met our inclusion criteria underscores the important variability across studies of CIN and HIV, including: different criteria for treating CIN lesions, different management techniques, different cut-offs for defining lesion detection at follow-up (low- or high-grade) and follow-up duration, differing biopsy indications and differences in the prevalence and adjustment of potential confounders. These perhaps contributed to the significant heterogeneity observed in some analyses. Also, most of the included studies were at medium-to-high risk of bias/confounding due to lack of adjustment of HIV-related time-dependent confounders such as CD4+ cell counts and HIV PVL.

Also, confounding by treatment indication[42] is inherent to ART studies conducted prior to the era of universal ART; this is because in these studies, women on ART were more likely to be of an advanced HIV clinical or immunological stage and perhaps more likely to have poorer CIN management outcomes as a consequence. This may have diluted the beneficial effect of ART or immune reconstitution in reducing the risk of CIN2+ detection at follow-up.

Another limitation was our inability to further explore the impact of the duration of ART use on the risk of CIN2+ detection at follow-up, as only one study investigated this[23]. This study found a non-significant paradoxical increase in the risk of CIN2+ detection at follow-up with increasing duration on ART (>2 years versus <2 years). These were however unadjusted estimates with a short follow-up duration (6 months) and there may also have been an influence of confounding by indication, as ART started at CD4+ counts <250 cells/μl. In a previous meta-analysis, long-term ART users (≥2 years) had a lower prevalence of CIN2+ compared with <2 years and ART-naïve combined[11]. It would have been interesting to see if this translates into a decreased risk of CIN2+ detection at follow-up following management and further help prioritize WLHIV who should be monitored more closely for detection at follow-up.

Despite the limitations, this is the first systematic review and meta-analysis to evaluate the association of ART and other HIV-related factors with CIN2+ detection at follow-up after CIN management among WLHIV. It included information from among nearly 1,500 WLHIV and several sub-analyses were done to investigate bias and heterogeneity. Although most of the included studies were carried out when ART was initiated at low CD4+ cell counts, these findings are still very useful especially for LMICs which have the highest burden of cervical cancer and where, despite the current push for universal ART, many WLHIV still present late to care.

Recommendations

Our findings support early ART i.e. starting ART for all WLHIV irrespective of CD4+ cell counts, as they will likely have better CIN management outcomes. The integration of cervical cancer screening and management into HIV care could be beneficial, such that WLHIV with CIN who are not adequately controlled with ART should be monitored at closer intervals for CIN2+ detection at follow-up of CIN management.

Going forward, there is a need for more consensus in treatment indications, definitions of lesion at follow-up ('treatment failure', 'recurrence', 'persistence'), minimum acceptable follow-up duration and CIN diagnostic methods. There is also need for longer term follow-up studies especially as women are being treated at increasingly higher CD4+ cell counts. These are important for future study designs and for a better understanding of the natural history of post-management CIN among WLHIV.

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Conflict of interest: The authors declare no potential conflicts of interest

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Figure 1: Study selection procedure

ART=antiretroviral therapy. **HIV PVL**=HIV plasma viral load. **CIN**=cervical intraepithelial neoplasia.

Figure 2: Meta-analysis of the association of ART on CIN2+ detection at follow-up (Analysis 1) and HIV PVL on CIN2+ detection at follow-up (Analysis 2)

ART= antiretroviral therapy. **PVL**=HIV plasma viral load**. n**=sample size. **cOR**=crude odds ratio. **aRR**=adjusted risk ratio. **aHR**=adjusted hazards ratio. **CIN2+**=Cervical Intraepithelial Neoplasia, grade 2 or higher. **Exposed**= 'ART' or 'Undetectable PVL'. **Unexposed**= 'ART-naïve' or 'detectable PVL'. In one study (Carlander, 2018), 77% of women had were managed using excisional methods and, in another study, (Heard, 2005), 85% of women had were managed using excisional methods.

Figure 3: Meta-analysis of the association of CD4+ cell count on CIN2+ detection at follow-up (Analysis 3)

Baseline CD4= CD4 at the time of CIN treatment. **Contemporary CD4**= CD4 at the time of CIN detection at follow-up. **Nadir CD4**= lowest CD4+ cell count ever recorded. **n**=sample size. **cOR**=crude odds ratio. **aRR**=adjusted risk ratio. **aHR**=adjusted hazards ratio. **CIN2+**=Cervical Intraepithelial Neoplasia, grade 2 or higher. In one study (Carlander, 2018), 77% of women had were managed using excisional methods.

Table 1: Characteristics of the 8 included studies representing 9 populations[A]

Author, year	Study design	Country	CIN grade at baseline*	n enrolled	Population characteristics	CIN management modality	FU duration, months[α]	Outcome definition
Babkina, 2015[21]	Cohort	USA (New Jersey)	CIN2+	44	Age[α]=44y	Conisation	24	**'Persistent or residual disease'** defined as CIN2/3 on repeat excision procedure or hysterectomy
Carlander, 2018[22]	Cohort	Sweden (Multisite)	CIN2+	140	Age[α]=34y; 65% on HAART; 53% with undetectable** HIV PVL	LLETZ, Laser conisation, CKC, Unspecified excision, Cryotherapy	7	**'Treatment failure'** defined as the presence of CIN2+ on cervical cytology/ histology at initial follow-up, within 1 year of treatment
De Vuyst, 2014[23]	Cohort	Kenya (Nairobi)	CIN2+	79	Age[α]=41 years; 77% on HAART; Median CD4+ =322/µl	Cryotherapy	6	**'Residual disease'** defined as histologically confirmed CIN2/3 at follow-up
Greene, 2019[24]	RCT	Kenya (Nairobi)	CIN2+	200	Age[α]=38 years; Median CD4+=371/µl; 86% on HAART; 63% with undetectable HIV PVL	Cryotherapy	24	**'Recurrence'** defined as cumulative post-management CIN2+ over a 24-month follow-up period following cryotherapy
Greene, 2019[24]	RCT	Kenya (Nairobi)	CIN2+	200	Age[α]=37 years; Median CD4+=385/µl; 92% on HAART; 65% with undetectable HIV PVL	LEEP	24	**'Recurrence'** defined as cumulative post-management CIN2+ over a 24-month follow-up period following LEEP

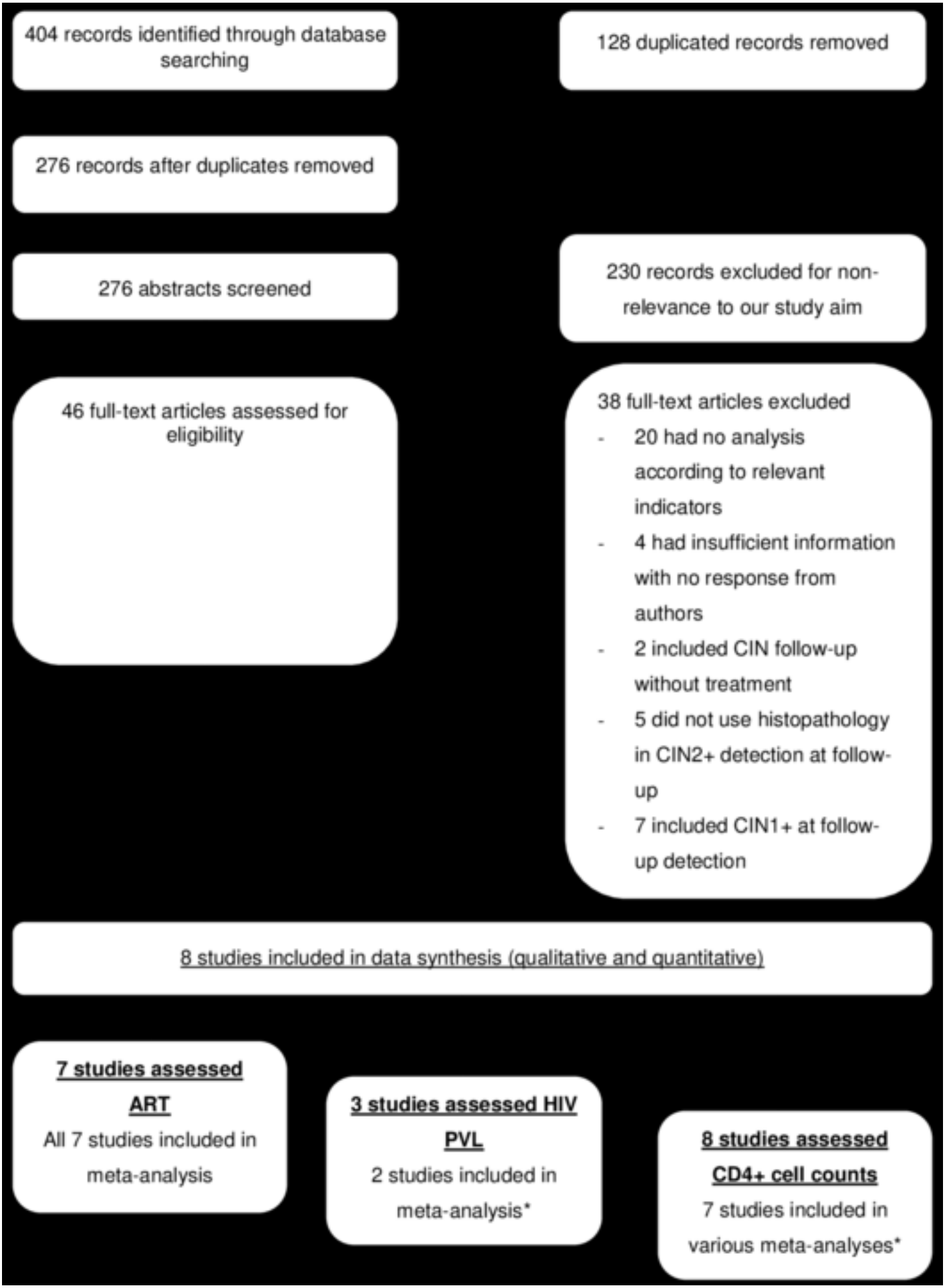
Author, year	Study design	Country	CIN grade at baseline*	n enrolled	Population characteristics	CIN management modality	FU duration, months$^{\alpha}$	Outcome definition
Heard, 2005[25]	Cohort	France (Paris)	CIN 2+	121	Age$^{\alpha}$=33 years; Median CD4+=327/µl; Median HIV-PVL = 499/ml	Laser vaporisation, LEEP	20	**'Recurrence'** defined as high-grade CIN post-treatment diagnosed within 3 months after surgery or, in the absence of biopsy, by at least 2 consecutive abnormal Papanicolaou smears associated with abnormal colposcopic findings
Huchko, 2014[26]	Cohort	Kenya (Kisumu)	CIN2+	283	Age$^{\alpha}$ =33 years; 65% on HAART; Median CD4+$^{\alpha}$ =418/µl	LEEP	6	**'Recurrence'** defined as CIN2+ within 12-months of CIN management
Orang'o, 2017[27]	Cohort	Kenya (Multisite)	VIA+	330	Age$^{\alpha}$=35 years; 87% on HAART; Median CD4+$^{\alpha}$ = 410/µl	Cryotherapy	11	**'Post-treatment detection at follow-up'** defined as biopsy- confirmed CIN2+ at follow-up ; women with negative VIA, Pap smear, and HR-HPV testing were assumed to be negative for CIN2+
Russomano, 2008[28]	Cohort	Brazil (Rio de Janeiro)	CIN2+	29	Age$^{\alpha}$=32 years; 85% on HAART; Median CD4+$^{\alpha}$ =557/µl	LEEP	33	**'Recurrence'** defined as biopsy-confirmed CIN2+ at follow-up

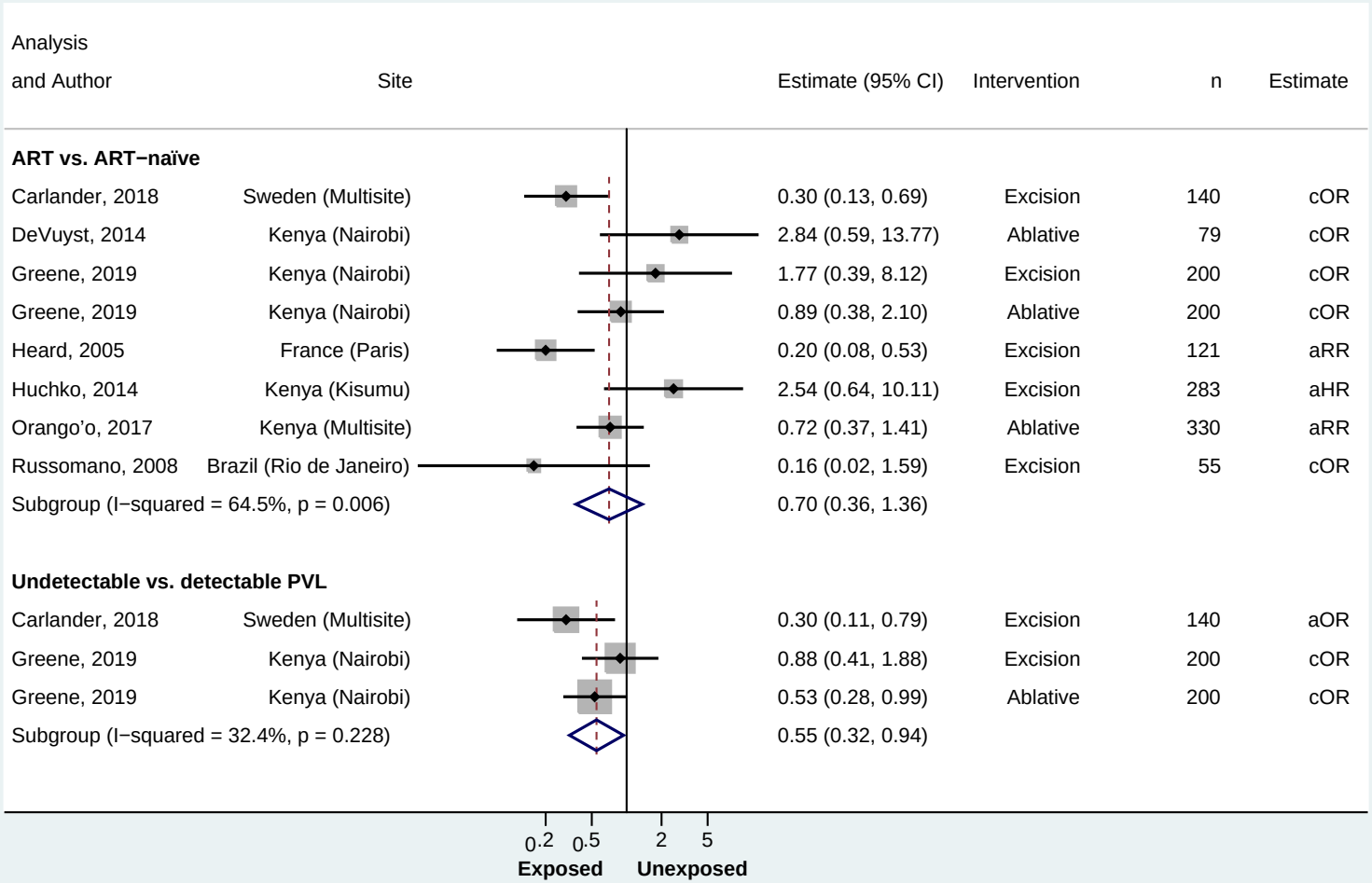
A=Arranged alphabetically**. n**=sample size. **FU**=follow-up. α=mean or median value. **CIN2+**=Cervical Intraepithelial Neoplasia, grade 2 or higher. **VIA+**=positive lesions on visual inspection with acetic acid. **LEEP**=Loop electrosurgical excision procedure. **LLETZ**=Large loop excision of the transformation zone. **CKC**=Cold knife conisation. **HAART**=Highly-active antiretroviral therapy (≥3 drugs belonging to at least 2 different drug classes). **HIV PVL**=HIV plasma viral load. *CIN grade at time of management. **<50copies/ml

Table 2: Stratified meta-analyses of association of HIV-related factors and CIN2+ detection at follow-up

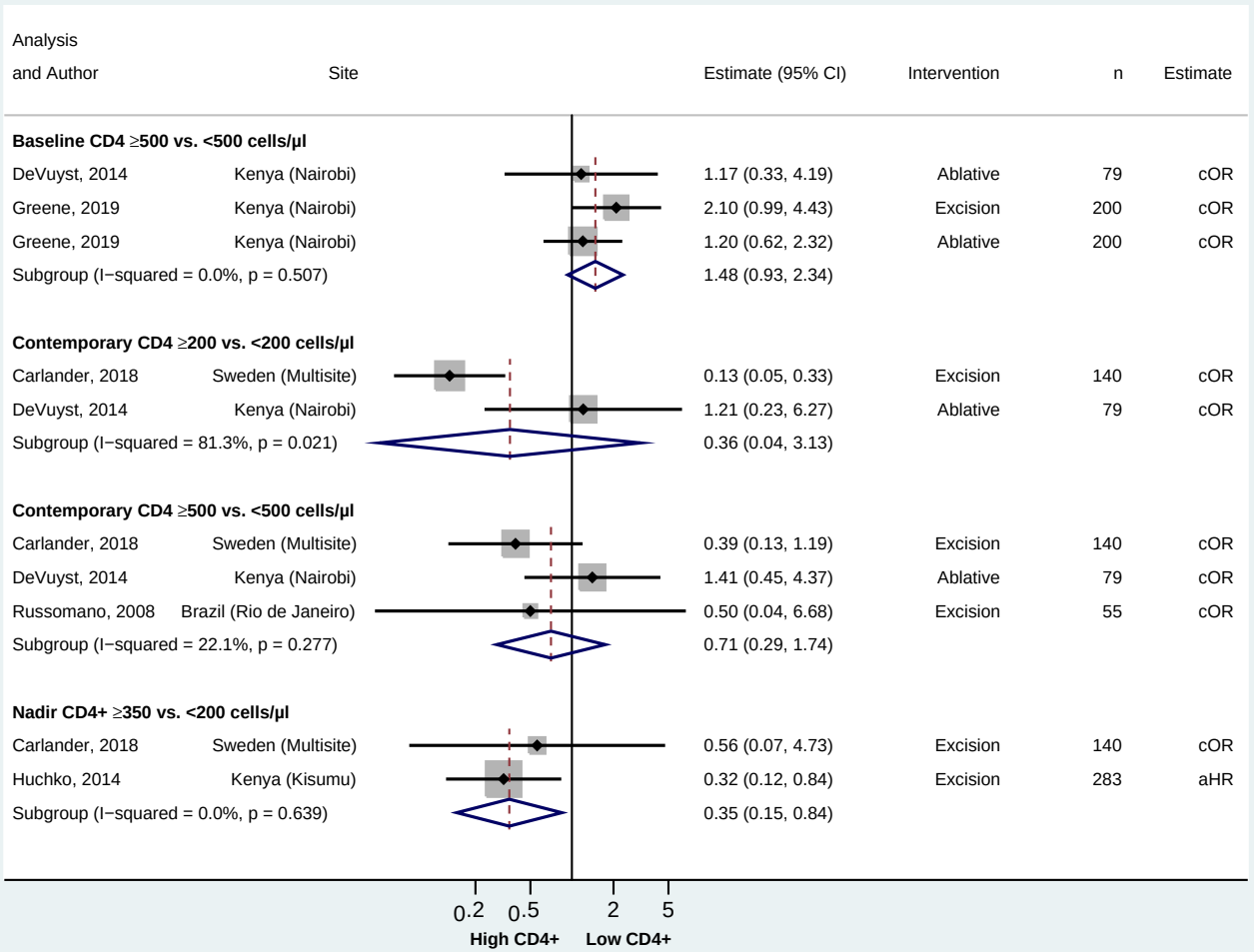
Criteria	Stratification	n populations	Estimate (95% CI)	I^2	P for heterogeneity
ART vs. ART naïve		**8**	**0.70 (0.36-1.36)**	**64.5%**	**0.006**
Country income	HMIC[22,25,28]	3	0.24 (0.13-0.45)	0.0%,	0.77
	LMIC[23,24,26,27]	5	1.13 (0.67-1.92)	18.8%	0.30
Follow-up duration	>12 months[24,25,28]	4	0.51 (0.17-1.52)	65.7%,	0.03
	≤12 months[22,23,26,27]	4	0.94 (0.36-2.45)	71.0%	0.02
Intervention	Ablative[23,24,27]	3	0.92 (0.52-1.65)	19.1%	0.29
	Excision[22,24–26,28]	5	0.53 (0.19-1.52)	70.4%	0.009
Undetectable vs. detectable HIV PVL (<50 vs ≥50 copies/ml)[22,24]		**3**	**0.55 (0.32-0.94)**	**32.4%**	**0.23**
CD4+ count, (cells/µl)					
Baseline CD4+	≥500 vs. <500[23,24]	3	1.48 (0.93-2.34)	0.0%	0.51
Contemporary CD4+	≥200 vs. <200[22,23]	2	0.36 (0.04-3.13)	81.3%	0.02
	≥500 vs. <500[22,23,28]	3	0.71 (0.29-1.74)	22.1%	0.28
	≥500 vs. <200[21,22,27]	3	0.68 (0.33-1.41)	10.4%	0.33
Nadir CD4+	≥350 vs. <200[22,26]	2	0.35 (0.15-0.84)	0.0%	0.64

ART=antiretroviral therapy. **HIV PVL**= HIV plasma viral load. **CIN**=cervical intraepithelial neoplasia. **CI**=confidence interval. **n**=number of studies. **HMIC**=High and upper-middle income countries. **LMIC**=Low and lower-middle income countries. **CIN2+**=Cervical Intraepithelial Neoplasia, grade 2 or higher. **Baseline CD4+**=CD4+ at the time of CIN treatment**. Contemporary CD4+=** CD4+ at the time of CIN detection at follow-up. **Nadir CD4+=** lowest recorded CD4+ *****= n+1 discrete study populations.





NOTE: Weights are from random−effects model



NOTE: Weights are from random−effects model