Anogenital warts and other HPV-associated anogenital lesions in the HIV-positive patient: a systematic review and meta-analysis of the efficacy and safety of interventions assessed in controlled clinical trials

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Online Supplement

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Abbreviations

AE – adverse events

APC – argon plasma coagulation

GRADE – Grading of Recommendations Assessment, Development and Evaluation

MID – minimal important difference

1. Methods

This systematic review and meta-analysis was part of a three-phase project. Part one has been published [doi: 10.1136/sextrans-2016-052768].[1] Similarities throughout the methods section may occur.

1.1. Search strategy

We comprehensively searched for reports of studies in the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and MEDLINE (including Medline in Process) on June 6th, 2016. The search covered inception of the databases through the date of the search. Terms for disease specification were combined with terms for HIV / immunocompromising conditions to be searched in the titles and abstracts. In MEDLINE and CENTRAL, MeSH-terms were used, and Emtree terms in Embase.

Full electronic search strategy (MEDLINE):

1. papillomavirus infections/ or warts/ or condylomata acuminata/
2. exp Alphapapillomavirus/
3. HPV.ab,kw,ti.
4. (papillomavirus or (papilloma adj virus)).ab,ti,kw.
5. "wart*".ab,kw,ti.
6. exp Precancerous Conditions/
7. "intraepithelial neoplasia".ab,kw,ti.
8. dysplasia.ab,kw,ti.
9. Carcinoma in Situ/
10. Bowen's Disease/
11. "bowen's disease".ab,kw,ti.
12. anogenital.ab,kw,ti.
13. anal.ab,kw,ti.
14. genital.ab,kw,ti.
15. genitoanal.ab,kw,ti.
16. "vulva*".ab,kw,ti.
17. perianal.ab,kw,ti.
18. "vagina*".ab,kw,ti.
19. (penis or penile).ab,kw,ti.
20. scrotal.ab,kw,ti.
21. mucocutaneous.ab,kw,ti.
22. venereal.ab,kw,ti.
23. perineal.ab,kw,ti.
24. exp condylomata acuminata/ or exp buschke-lowenstein tumor/
25. "condyloma* acuminat* ".ab,kw,ti.
26. "condyloma*".ab,kw,ti.
27. "Buschke-Lowenstein tumor".ab,kw,ti.
28. "bowenoid papulosis".ab,kw,ti.
29. erythroplasia.ab,kw,ti.
30. exp Erythroplasia/
31. Anus Neoplasms/
32. exp Penile Neoplasms/
33. exp Vaginal Neoplasms/
34. exp Vulvar Neoplasms/
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
36. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
37. 35 and 36
38. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
39. 37 or 38
40. exp Immunosuppression/
41. Immunocompromised Host/
42. exp HIV Infections/
43. exp Leukemia/
44. HIV.ab,kw,ti.

45. "human immunodeficiency virus".ab,kw,ti.
46. "immunosuppress*".ab,kw,ti.
47. "immunocompromi*".ab,kw,ti.
48. AIDS.ab,kw,ti.
49. "acquired immunodeficiency syndrome".ab,kw,ti.
50. "organ transplant* ".ab,kw,ti.
51. leukemia.ab,kw,ti.
52. "stem cell transplant* ".ab,kw,ti.
53. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. 39 and 53

1.2. Data items

The following data items were extracted: 1) study population (inclusion / exclusion criteria, number of participants randomized, localization and extent of the lesions, gender, age, previous treatments, smoking, sexual behaviour: orientation, promiscuity), 2) baseline data on the immunocompromising condition (e.g. CD4 cell counts), 3) length of follow-up, 4) outcomes assessed, and 5) results (predefined outcomes).

1.3. GRADE evaluations: downgrading the quality of the evidence

The quality of the evidence was evaluated on the outcome level according to the GRADE approach for each comparison of interventions that was available.[2] If the contributing studies were randomized trials, the quality of the evidence started with “high”. For observational studies such as clinically controlled studies, the quality of the evidence started with “very low” and could be rated up, when the studies showed a large magnitude of effect, a dose-response gradient, or if plausible confounding increased the confidence in the estimate of effect.[3] The quality rating was downgraded in the presence of risk of bias,[4, 5] inconsistency,[6] indirectness,[7] imprecision,[8] and publication bias.[9]

1.3.1. Downgrading due to risk of bias

For the GRADE evaluations of the risk of bias (referring to the outcome level), the previously determined risk of bias at the study level (“Cochrane Collaboration’s tool for assessing risk of bias in randomized trials” [5]) of the contributing studies was considered. .

1.3.2. Downgrading due to inconsistency

When more than one study contributed data for an overall estimate of effect, the individual study results were evaluated for their consistency. This evaluation was both based on visual inspection of the effect estimates and their 95% confidence intervals, and on the evaluation of the I^2 statistic which quantifies the proportion of the variation in the point estimates due to among-study-differences.[6] Grading the quality of the evidence down due to inconsistency was considered in the presence of widely varying point estimates, minimal or no overlap of confidence intervals or $I^2 > 50\%$.[6] Consistency could not be evaluated if only one study contributed data; in this case, no downgrading due to inconsistency was performed.

1.3.3. Downgrading due to indirectness

According to the GRADE guidelines, directness depends on the participants, interventions and outcomes of the included studies[7]. Since these parameters were determined by the inclusion criteria of the present systematic review, usually no downgrading due to indirectness of the results needed to be performed. In the case that an outcome included data from studies with a significant amount of participants who had both anogenital warts and intraepithelial neoplasia, the quality of the evidence could be downgraded due to indirectness.

1.3.4. Downgrading due to imprecision

The precision of the calculated estimates of effect was evaluated in consideration of two criteria: 1) clinical importance of differences between interventions as based upon a predefined

threshold of a “minimal important difference” (MID threshold) as previously reported,[10] and 2) size of the confidence interval.[11]

For estimates of effect calculated as relative risks (binary outcomes), the MID threshold was defined as the line of no effect +/- 0.25 (i.e. 0.75 and 1.25). We considered a statistically significant effect of an intervention imprecise, if the confidence interval crossed the MID threshold (i.e., the effect was statistically significant but of questionable clinical significance). If the effect was statistically significant but did not cross the MID threshold (i.e., statistically significant and supposedly clinically significant) or if the effect was statistically insignificant and did not cross the MID threshold (i.e., no statistically or clinically significant difference between the interventions), no downgrading due to imprecision was performed.

We additionally considered the estimate of effect imprecise if the magnitude of its 95% confidence interval exceeded 0.01 or 100.

1.3.5. Downgrading due to publication bias

Trial registers were not performed, and therefore our assessment of publication bias could solely be based upon the assessment of funnel plots. An evaluation of funnel plots is generally only considered meaningful if more than ten trials contribute data for a meta-analysis. Publication bias was consequently evaluated as ‘undetected’, in the case that less than ten trials contributed data for a meta-analysis.

2. Results

2.1. Reasons for the exclusion of studies during full-text assessment

Table 1 gives details of the reasons for the exclusion of studies during the full-text assessment.

Table 1: Reasons for exclusion of studies during fulltext assessment

Study	Reason for exclusion
Anderson et al. 2009[12]	P: participants did not have to have lesions or positive cytology, high-risk HPV infection could also be latent
Bonatti et al. 2007[13]	S: uncontrolled case-series
Bradbury et al. 2016[14]	O: outcomes not reported separately for the different treatment modalities
Carmen Cruz Perez et al. 2011[15]	P: participants not immunosuppressed, no anogenital warts
Cranston et al. 2014[16]	O: only baseline data reported
Deshmukh et al. 2015[17]	Other: no original data reported
Duray et al. 2013[18]	other: only abstract available, not enough information supplied
Frega et al. 2013[19]	P: participants not immunocompromised
Giacomet et al. 2014[20]	P: no HPV-associated disease at baseline
Gilson et al. 1999[21]	other: only abstract available, data reported in Gilson et al. 1999[22]
Gupta et al. 2013[23]	P: participants not immunocompromized
Gupta et al. 2008[24]	S: uncontrolled cohort study
Herrera et al. 2007[25]	S: uncontrolled cohort study
Isik et al. 2014[26]	P: participants not immunocompromized
Krebs et al. 1986[27]	P: 11/16 prospectively studied participants had exclusively the cervix involved; I: treatment modalities unclear; S: mixed retrospective and prospective patients
Kreuter et al. 2008[28]	S: uncontrolled cohort study (follow-up of cleared patients from Wieland et al. 2006[29])
Lacey et al. 2003[30]	P: participants not immunocompromized
Maiman et al. 1999[31]	P: cervical IEN
Maiman et al. 1999[32]	Duplicate
Pelletier et al. 2004[33]	P: no clinically manifest, but latent HPV infection
Safrin et al. 1997[34]	Other: no original data
Saiag et al. 2009[35]	S: uncontrolled cohort study
Sanclemente et al. 2007[36]	S: uncontrolled cohort study
Sawaya et al. 2008[37]	P: participants not immunocompromized
Sendagorta et al. 2016[38]	S: uncontrolled cohort study
Sendagorta et al. 2015[39]	S: uncontrolled cohort study, only abstract available (full data reported in Sendagorta et al. 2016[38])
Sirera et al. 2013[40]	S: uncontrolled retrospective cohort study
Smulian et al. 2014[41]	S: uncontrolled cohort study
Stefanaki et al. 2008[42]	P: participants not immunocompromized
Stefanaki et al. 2008[43]	P: participants not immunocompromized
Stier et al. 2008[44]	S: uncontrolled cohort study
Stier et al. 2013[45]	S: uncontrolled cohort study
Swinehart et al. 1997[46]	P: participants not immunocompromized
Taylor et al. 2010[47]	P: cervical IEN
Weis et al. 2012[48]	other: several patients are reported twice, data are not reported separately for this subgroup; outcome assessment not at the time of interest (control group: mean, 1.79 years, interventional group: mean, 1.28 years)
Wieland et al. 2006[29]	S: uncontrolled cohort study
Wilkin et al. 2010[49]	S: uncontrolled cohort study, P: no signs of HPV infection at baseline

P, study population not relevant for the systematic review; O, outcomes not relevant for the systematic review; S, study design not appropriate for inclusion; other, other reasons for exclusion.

2.2. Risk of bias

The risk of bias of the included studies was heterogeneous. Two studies were clinically controlled studies,[50, 51] and of the nine randomized controlled trials,[22, 52-58] only three[52, 56, 58] adequately reported the methods of sequence generation. Four studies[22, 53, 54, 59] were evaluated as being at low risk of performance bias due to the information given with respect to blinding of participants, whereas the other studies were deemed to be at high risk. Detection bias was rated as low in two studies[52, 53] and as high in eight studies.[50, 51, 54-59] Attrition bias was evaluated as low in the majority of studies.[22, 50, 51, 54-56, 58] Two studies[52, 53] were rated as being at high risk due to the exclusion of dropouts from the analysis combined with insufficient information on the dropouts' group assignments. A study protocol was only available for one trial[56] which was evaluated as being at low risk of selective reporting. Selective reporting was evaluated as unclear for the majority of trials and as high for one study[50] due to missing outcome data for one group. Seven studies[50, 52, 54, 55, 57-59] were rated as being at a high risk of other biases, which are specifically discussed for each comparison.

Figure 1 provides an overview of the risk of bias evaluations for the included studies. A detailed presentation of the risk of bias evaluations for each study is presented within the original publication.

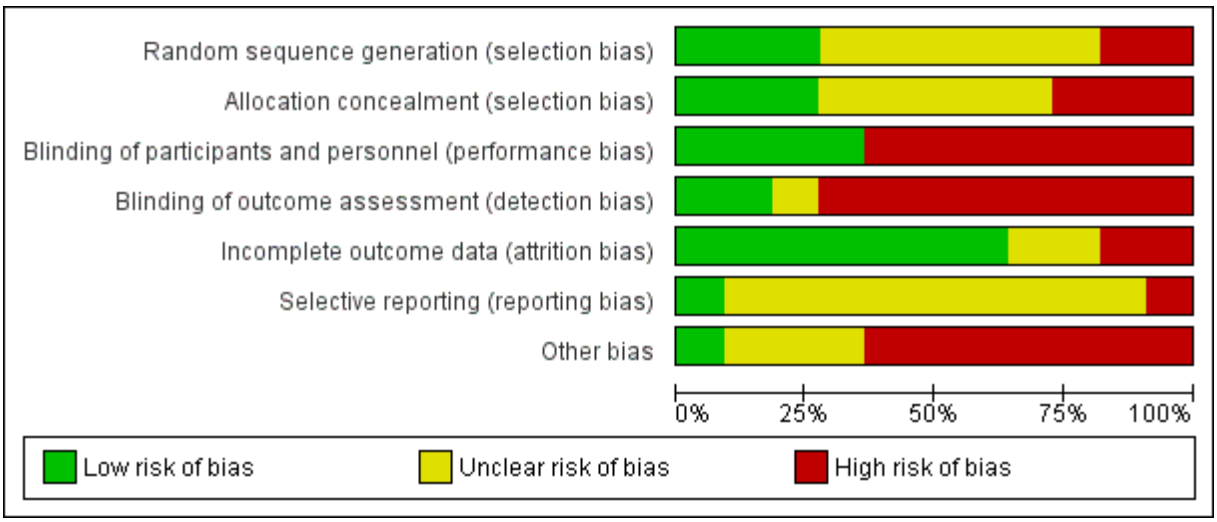

Figure 1: Risk of Bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

2.3. Imiquimod 5% cream vs. placebo

Table 2: Summary of findings: imiquimod 5% cream vs. placebo

Imiquimod 5% cream compared to placebo											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Imiquimod 5% cream**		**Risk with placebo**	**Risk difference with Imiquimod 5% cream**
Short-term complete clearance (4w after EOT +/-4w) – Pooled results (external AGW and high-grade AIN)											
153 (2 RCTs)	not serious	not serious	serious [1]	serious [2]	none	⨁⨁◯◯ LOW	3/60 (5.0%)	11/93 (11.8%)	**RR 2.34** (0.68 to 8.04)	50 per 1.000	**67 more per 1.000** (16 fewer to 352 more)
Short-term complete clearance (4w after EOT +/-4w) - External AGW											
100 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	2/35 (5.7%)	7/65 (10.8%)	**RR 1.88** (0.41 to 8.59)	57 per 1.000	**50 more per 1.000** (34 fewer to 434 more)
Short-term complete clearance (4w after EOT +/-4w) - High grade AIN											
53 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	1/25 (4.0%)	4/28 (14.3%)	**RR 3.57** (0.43 to 29.87)	40 per 1.000	**103 more per 1.000** (23 fewer to 1.155 more)
Reduction in disease severity - External AGW: Partial clearance (≥50% clearance) at EOT											

Imiquimod 5% cream compared to placebo											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Imiquimod 5% cream**		**Risk with placebo**	**Risk difference with Imiquimod 5% cream**
100 (1 RCT)	not serious	not serious	not serious	serious [3]	none	⨁⨁⨁◯ MODERATE	5/35 (14.3%)	25/65 (38.5%)	**RR 2.69** (1.13 to 6.41)	143 per 1.000	**241 more per 1.000** (19 more to 773 more)
Reduction in disease severity - High grade AIN: Downgrading in cytology (HSIL --> LSIL) 8 months after EOT											
53 (1 RCT)	not serious	not serious	not serious	very serious [4]	none	⨁⨁◯◯ LOW	0/25 (0.0%)	8/28 (28.6%)	**RR 15.24** (0.92 to 251.29)	20 per 1.000	**285 more per 1.000** (2 fewer to 5006 more)
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT +/- 16w) - High grade AIN											
5 (1 RCT)	-	-	-	-	-	-	0/1 (0.0%)	0/4 (0.0%)	not estimable	not estimable	
Long-term recurrence (12m after EOT +/- 2m) - High grade AIN											
5 (1 RCT)	-	-	-	-	-	-	0/1 (0.0%)	0/4 (0.0%)	not estimable	not estimable	
Quality of life after EOT											

Imiquimod 5% cream compared to placebo

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With Imiquimod 5% cream	Relative effect (95% CI)	Risk with placebo	Risk difference with Imiquimod 5% cream
No data available											
Dropouts due to adverse events											
153 (2 RCTs)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	1/60 (1.7%)	2/93 (2.2%)	**RR 1.08** (0.14 to 8.52)	17 per 1.000	**1 more per 1.000** (14 fewer to 125 more)
Pain during treatment - External AGW											
92 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	1/30 (3.3%)	1/62 (1.6%)	**RR 0.48** (0.03 to 7.47)	33 per 1.000	**17 fewer per 1.000** (32 fewer to 216 more)
Local AE: erythema / inflammation / skin irritation - External AGW											
92 (1 RCT)	not serious	not serious	not serious	very serious [5]	none	⨁⨁◯◯ LOW	0/30 (0.0%)	10/62 (16.1%)	**RR 10.33** (0.63 to 170.65)	17 per 1.000 [6]	**159 more per 1.000** (6 fewer to 2884 more) [6]
Local AE: erosion / excoriation / ulceration - External AGW											
92 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	0/30 (0.0%)	5/62 (8.1%)	**RR 5.41** (0.31 to 94.79)	17 per 1.000 [6]	**75 more per 1.000** (12 fewer to 1594 more) [6]
Progressive disease with respect to grade of dysplasia - High grade AIN											

Imiquimod 5% cream compared to placebo											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Imiquimod 5% cream**		**Risk with placebo**	**Risk difference with Imiquimod 5% cream**
54 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	1/26 (3.8%)	0/28 (0.0%)	**RR 0.31** (0.01 to 7.30)	38 per 1.000	**27 fewer per 1.000** (38 fewer to 242 more)

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Pooled effect estimate from two studies with different population (AGW, IEN)
2. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25
3. Confidence interval crosses minimal important difference threshold of 1.25
4. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25; very large confidence interval
5. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25; very large confidence interval
6. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo group. The calculation of the risk in the imiquimod group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.4. Imiquimod 5% cream vs. electrocautery

Table 3: Summary of findings: imiquimod 5% cream vs. electrocautery

Imiquimod 5% cream compared to electrocautery											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With electrocautery	**With Imiquimod 5% cream**		**Risk with electrocautery**	**Risk difference with Imiquimod 5% cream**
Short-term complete clearance (4w after EOT) – Histological clearance (intra- and perianal AIN)											
88 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	18/46 (39.1%)	13/54 (24.1%)	**RR 0.62** (0.34 to 1.12)	391 per 1.000	**149 fewer per 1.000** (258 fewer to 45 more)
Short-term complete clearance (4w after EOT) - Intraanal AIN											
75 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	16/34 (47.1%)	9/41 (22.0%)	**RR 0.47** (0.24 to 0.92)	471 per 1.000	**249 fewer per 1.000** (358 fewer to 38 fewer)
Short-term complete clearance (4w after EOT) - Perianal AIN											
13 (1 RCT)	not serious	not serious	not serious	serious [3]	none	⨁⨁⨁◯ MODERATE	3/4 (75.0%)	9/9 (100.0%)	**RR 1.36** (0.75 to 2.45)	750 per 1.000	**270 more per 1.000** (188 fewer to 1.088 more)
Reduction in disease severity: Downgrading or clearance of high grade AIN											

Imiquimod 5% cream compared to electrocautery

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electrocautery	With Imiquimod 5% cream	Relative effect (95% CI)	Risk with electrocautery	Risk difference with Imiquimod 5% cream
43 (1 RCT)	not serious	not serious	not serious	serious [4]	none	⨁⨁⨁◯ MODERATE	13/19 (68.4%)	11/24 (45.8%)	**RR 0.67** (0.39 to 1.14)	684 per 1.000	**226 fewer per 1.000** (417 fewer to 96 more)
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT) - Intra- and perianal AIN											
37 (1 RCT)	not serious	not serious	not serious	serious [5]	none	⨁⨁⨁◯ MODERATE	3/21 (14.3%)	3/16 (18.8%)	**RR 1.31** (0.30 to 5.66)	143 per 1.000	**44 more per 1.000** (100 fewer to 666 more)
Long-term recurrence (48w after EOT) - Intra- and perianal AIN											
36 (1 RCT)	not serious	not serious	not serious	serious [5]	none	⨁⨁⨁◯ MODERATE	9/21 (42.9%)	7/15 (46.7%)	**RR 1.09** (0.52 to 2.27)	429 per 1.000	**39 more per 1.000** (206 fewer to 544 more)
Quality of life after EOT											
No data available											

Imiquimod 5% cream compared to electrocautery												
Quality assessment							**Summary of findings**					
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With electrocautery	**With Imiquimod 5% cream**		**Risk with electrocautery**	**Risk difference with Imiquimod 5% cream**
Dropouts due to adverse events - Intra- and perianal AIN											
100 (1 RCT)	not serious	not serious	not serious	serious [5]	none	⨁⨁⨁◯ MODERATE	3/46 (6.5%)	5/54 (9.3%)	**RR 1.42** (0.36 to 5.62)	65 per 1.000	**27 more per 1.000** (42 fewer to 301 more)
Pain during treatment - Intra- and perianal AIN											
98 (1 RCT)	not serious	not serious	not serious	serious [3]	none	⨁⨁⨁◯ MODERATE	27/45 (60.0%)	37/53 (69.8%)	**RR 1.16** (0.86 to 1.57)	600 per 1.000	**96 more per 1.000** (84 fewer to 342 more)
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75
2. Confidence interval crosses minimal important difference threshold of 0.75
3. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25

4. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75
5. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25

2.5. Imiquimod 5% cream vs. 5-Fluorouracil 2% cream

Table 4: Summary of findings: imiquimod 5% cream vs. 5-fluorouracil 2% cream

Imiquimod 5% cream compared to 5-fluorouracil 2% cream												
Quality assessment							**Summary of findings**					
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With 5-fluorouracil 2% cream	**With Imiquimod 5% cream**		**Risk with 5-fluorouracil 2% cream**	**Risk difference with Imiquimod 5% cream**
Short-term complete clearance (4w after EOT) – Histological clearance (intra- and perianal AIN)											
99 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	8/48 (16.7%)	13/54 (24.1%)	**RR 1.44** (0.66 to 3.18)	167 per 1.000	**73 more per 1.000** (57 fewer to 364 more)
Short-term complete clearance (4w after EOT) - Intraanal AIN											
83 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	7/42 (16.7%)	9/41 (22.0%)	**RR 1.32** (0.54 to 3.20)	167 per 1.000	**53 more per 1.000** (77 fewer to 367 more)
Short-term complete clearance (4w after EOT) - Perianal AIN											
16 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	4/7 (57.1%)	9/9 (100.0%)	**RR 1.69** (0.90 to 3.16)	571 per 1.000	**394 more per 1.000** (57 fewer to 1.234 more)
Reduction in disease severity: Downgrading or clearance of high grade AIN											

Imiquimod 5% cream compared to 5-fluorouracil 2% cream											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With 5-fluorouracil 2% cream	**With Imiquimod 5% cream**		**Risk with 5-fluorouracil 2% cream**	**Risk difference with Imiquimod 5% cream**
52 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	12/28 (42.9%)	11/24 (45.8%)	**RR 1.07** (0.58 to 1.97)	429 per 1.000	**30 more per 1.000** (180 fewer to 416 more)
Reduction in disease severity: Downgrading or clearance of high grade AIN - High grade AIN: histological downgrading or clearance											
52 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	12/28 (42.9%)	11/24 (45.8%)	**RR 1.07** (0.58 to 1.97)	429 per 1.000	**30 more per 1.000** (180 fewer to 416 more)
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT) - Intra- and perianal AIN											
29 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	5/13 (38.5%)	3/16 (18.8%)	**RR 0.49** (0.14 to 1.67)	385 per 1.000	**196 fewer per 1.000** (331 fewer to 258 more)
Long-term recurrence (48w after EOT) - Intra- and perianal AIN											

Imiquimod 5% cream compared to 5-fluorouracil 2% cream

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With 5-fluorouracil 2% cream	With Imiquimod 5% cream	Relative effect (95% CI)	Risk with 5-fluorouracil 2% cream	Risk difference with Imiquimod 5% cream
27 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	6/12 (50.0%)	7/15 (46.7%)	**RR 0.93** (0.43 to 2.04)	500 per 1.000	**35 fewer per 1.000** (285 fewer to 520 more)
Quality of life after EOT											
No data available											
Dropouts due to adverse events - Intra- and perianal AIN											
102 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	2/48 (4.2%)	5/54 (9.3%)	**RR 2.22** (0.45 to 10.93)	42 per 1.000	**51 more per 1.000** (23 fewer to 414 more)
Pain during treatment - Intra- and perianal AIN											
101 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	32/48 (66.7%)	37/53 (69.8%)	**RR 1.05** (0.80 to 1.37)	667 per 1.000	**33 more per 1.000** (133 fewer to 247 more)
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25
2. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25

2.6.5-Fluorouracil 2% cream vs. electrocautery

Table 5: Summary of findings: 5-fluorouracil 2% cream vs. electrocautery

5-fluorouracil 2% cream compared to electrocautery											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With electrocautery	**With 5-fluorouracil 2% cream**		**Risk with electrocautery**	**Risk difference with 5-fluorouracil 2% cream**
Short-term complete clearance (4w after EOT) – Histological clearance (intra- and perianal AIN)											
87 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	18/46 (39.1%)	8/48 (16.7%)	**RR 0.43** (0.21 to 0.88)	391 per 1.000	**223 fewer per 1.000** (309 fewer to 47 fewer)
Short-term complete clearance (4w after EOT) - Intraanal AIN											
76 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	16/34 (47.1%)	7/42 (16.7%)	**RR 0.35** (0.16 to 0.76)	471 per 1.000	**306 fewer per 1.000** (395 fewer to 113 fewer)
Short-term complete clearance (4w after EOT) - Perianal AIN											
11 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	3/4 (75.0%)	4/7 (57.1%)	**RR 0.76** (0.32 to 1.79)	750 per 1.000	**180 fewer per 1.000** (510 fewer to 593 more)
Reduction in disease severity: Downgrading or clearance of high grade AIN											

5-fluorouracil 2% cream compared to electrocautery

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electrocautery	With 5-fluorouracil 2% cream	Relative effect (95% CI)	Risk with electrocautery	Risk difference with 5-fluorouracil 2% cream
47 (1 study)	not serious	not serious	not serious	serious [3]	none	⊕⊕⊕◯ MODERATE	13/19 (68.4%)	12/28 (42.9%)	**RR 0.63** (0.37 to 1.06)	684 per 1.000	**253 fewer per 1.000** (431 fewer to 41 more)
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT) - Intra- and perianal AIN											
34 (1 RCT)	not serious	not serious	not serious	serious [4]	none	⊕⊕⊕◯ MODERATE	3/21 (14.3%)	5/13 (38.5%)	**RR 2.69** (0.77 to 9.43)	143 per 1.000	**241 more per 1.000** (33 fewer to 1.204 more)
Long-term recurrence (48w after EOT) - Intra- and perianal AIN											
33 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	9/21 (42.9%)	6/12 (50.0%)	**RR 1.17** (0.55 to 2.47)	429 per 1.000	**73 more per 1.000** (193 fewer to 630 more)
Quality of life after EOT											
No data available											

5-fluorouracil 2% cream compared to electrocautery

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electrocautery	With 5-fluorouracil 2% cream	Relative effect (95% CI)	Risk with electrocautery	Risk difference with 5-fluorouracil 2% cream
Dropouts due to adverse events - Intra- and perianal AIN											
94 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	3/46 (6.5%)	2/48 (4.2%)	**RR 0.64** (0.11 to 3.65)	65 per 1.000	**23 fewer per 1.000** (58 fewer to 173 more)
Pain during treatment - Intra- and perianal AIN											
93 (1 RCT)	not serious	not serious	not serious	serious [4]	none	⨁⨁⨁◯ MODERATE	27/45 (60.0%)	32/48 (66.7%)	**RR 1.11** (0.81 to 1.52)	600 per 1.000	**66 more per 1.000** (114 fewer to 312 more)
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Confidence interval crosses minimal important difference threshold of 0.75
2. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25
3. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75

4. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25

2.7. Cidofovir 1% cream vs. placebo

Table 6: Summary of findings: Cidofovir 1% cream vs. placebo

Cidofovir 1% cream compared to placebo											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Cidofovir 1% cream**		**Risk with placebo**	**Risk difference with Cidofovir 1% cream**
Short-term complete clearance (4w after EOT +/-4w)											
No data available											
Reduction in disease severity: partial clearance at 2w after EOT - External AGW: Partial clearance (≥50% clearance) at 2w after EOT											
12 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	0/6 (0.0%)	3/6 (50.0%)	**RR 7.00** (0.44 to 111.91)	83 per 1.000 [4]	**498 more per 1.000** (46 fewer to 9206 more) [4]
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT +/- 16w)											
No data available											
Long-term recurrence (12m after EOT +/- 2m)											

Cidofovir 1% cream compared to placebo

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With Cidofovir 1% cream	Relative effect (95% CI)	Risk with placebo	Risk difference with Cidofovir 1% cream
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events											
No data available											
Pain during treatment - External AGW											
12 (1 RCT)	serious [1]	not serious	not serious	serious [3]	none	⨁⨁◯◯ LOW	0/6 (0.0%)	1/6 (16.7%)	**RR 3.00** (0.15 to 61.74)	83 per 1.000 [4]	**166 more per 1.000** (71 fewer to 5041 more) [4]
Local AE: erythema / inflammation / skin irritation - External AGW											
12 (1 RCT)	serious [1]	not serious	not serious	very serious [2]	none	⨁◯◯◯ VERY LOW	0/6 (0.0%)	3/6 (50.0%)	**RR 7.00** (0.44 to 111.91)	83 per 1.000 [4]	**498 more per 1.000** (46 fewer to 9206 more) [4]
Local AE: erosion / excoriation / ulceration - External AGW											
12 (1 RCT)	serious [1]	not serious	not serious	serious [3]	none	⨁⨁◯◯ LOW	0/6 (0.0%)	2/6 (33.3%)	**RR 5.00** (0.29 to 86.43)	83 per 1.000 [4]	**332 more per 1.000** (59 fewer to 7091 more) [4]
Progressive disease with respect to grade of dysplasia											

Cidofovir 1% cream compared to placebo

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With placebo	With Cidofovir 1% cream	Relative effect (95% CI)	Risk with placebo	Risk difference with Cidofovir 1% cream
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Other sources of bias: Very low sample size, baseline data on HIV severity indicate group differences
2. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25; very large confidence interval
3. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25
4. Due to zero observed events, the anticipated risk in the placebo group is based on a correction of 0.5 observed events in the placebo group. The calculation of the risk in the cidofovir group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the placebo group.

2.8. Cidofovir 1% gel vs. electrocautery

Table 7: Summary of findings: Cidofovir 1% gel vs. electrocautery

Cidofovir 1% gel compared to electrocautery											
Quality assessment							**Summary of findings**				
							Study event rates (%)			**Anticipated absolute effects**	
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With electrocautery**	**With Cidofovir 1% gel**	**Relative effect (95% CI)**	**Risk with electrocautery**	**Risk difference with Cidofovir 1% gel**
Short-term complete clearance (after EOT) - External AGW											
55 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	27/29 (93.1%)	20/26 (76.9%)	**RR 0.83** (0.65 to 1.04)	931 per 1.000	**158 fewer per 1.000** (326 fewer to 37 more)
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (6m after EOT) - External AGW											
36 (1 study)	serious [1]	not serious	not serious	serious [3]	none	⨁⨁◯◯ LOW	14/19 (73.7%)	6/17 (35.3%)	**RR 0.48** (0.24 to 0.96)	737 per 1.000	**383 fewer per 1.000** (560 fewer to 29 fewer)

Cidofovir 1% gel compared to electrocautery

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electrocautery	With Cidofovir 1% gel	Relative effect (95% CI)	Risk with electrocautery	Risk difference with Cidofovir 1% gel
Long-term recurrence (12m after EOT +/- 2m)											
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events											
No data available											
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of performance and detection bias; unclear risk of selection bias
2. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75
3. Confidence interval crosses minimal important difference threshold of 0.75

2.9. IFN alpha-2b (systemical) vs. IFN beta (systemical)

Table 8: Summary of findings: IFN alpha-2b (systemical) vs. IFN beta (systemical)

IFN alpha-2b (systemical) compared to IFN beta (systemical)												
Quality assessment							**Summary of findings**					
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With IFN beta (systemical)	**With IFN alpha-2b (systemical)**		**Risk with IFN beta (systemical)**	**Risk difference with IFN alpha-2b (systemical)**
Short-term complete clearance (4w after EOT +/-4w)											
No data available											
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (6m after EOT) - HPV genital lesions of the lower genital tract, not further specified											
17 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	4/8 (50.0%)	4/9 (44.4%)	**RR 0.89** (0.32 to 2.43)	500 per 1.000	**55 fewer per 1.000** (340 fewer to 715 more)
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT +/- 16w)											
No data available											
Long-term recurrence (12m after EOT +/- 2m)											

IFN alpha-2b (systemical) compared to IFN beta (systemical)

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With IFN beta (systemical)	With IFN alpha-2b (systemical)	Relative effect (95% CI)	Risk with IFN beta (systemical)	Risk difference with IFN alpha-2b (systemical)
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events - HPV genital lesions of the lower genital tract, not further specified											
17 (1 study)	-	-	-	-	-	-	0/8 (0.0%)	0/9 (0.0%)	not estimable	not estimable	
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of performance and detection bias; unclear risk of selection bias
2. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25

2.10. Imiquimod 5% cream plus argon plasma coagulation (APC) vs. APC

Table 9: Summary of findings: Imiquimod 5% cream plus argon plasma coagulation vs. argon plasma coagulation

Imiquimod 5% cream + argon plasma coagulation compared to argon plasma coagulation alone												
Quality assessment							**Summary of findings**					
							Study event rates (%)			**Anticipated absolute effects**		
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With argon plasma coagulation**	**With Imiquimod 5% cream + argon plasma coagulation**	**Relative effect (95% CI)**	**Risk with argon plasma coagulation**	**Risk difference with Imiquimod 5% cream + argon plasma coagulation**
Short-term complete clearance (4w after EOT) - Intraanal warts												
13 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	7/7 (100.0%)	6/6 (100.0%)	**RR 1.00** (0.76 to 1.31)	1.000 per 1.000	**0 fewer per 1.000** (240 fewer to 310 more)
Reduction in disease severity: partial clearance at EOT												
No data available												
Intermediate-term complete clearance (24w after EOT +/-16w)												
No data available												
Long-term complete clearance (12m after EOT +/-2m)												
No data available												
Intermediate-term recurrence (24w after EOT +/- 16w)												
No data available												

Imiquimod 5% cream + argon plasma coagulation compared to argon plasma coagulation alone												
Quality assessment							**Summary of findings**					
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With argon plasma coagulation	**With Imiquimod 5% cream + argon plasma coagulation**		**Risk with argon plasma coagulation**	**Risk difference with Imiquimod 5% cream + argon plasma coagulation**
Long-term recurrence (mean follow-up 11.4 months) - Intraanal warts											
13 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	5/7 (71.4%)	3/6 (50.0%)	**RR 0.70** (0.28 to 1.77)	714 per 1.000	**214 fewer per 1.000** (514 fewer to 550 more)
Quality of life after EOT											
No data available											
Dropouts due to adverse events - Intraanal warts											
13 (1 study)	-	-	-	-	-	-	0/7 (0.0%)	0/6 (0.0%)	not estimable	not estimable	
Pain during treatment - Intraanal warts											
13 (1 study)	-	-	-	-	-	-	0/7 (0.0%)	0/6 (0.0%)	not estimable	not estimable	
Local AE: erythema / inflammation / skin irritation - Intraanal warts											
49 (1 RCT)	not serious	not serious	not serious	serious [3]	none	⨁⨁⨁◯ MODERATE	0/25 (0.0%)	10/24 (41.7%)	**RR 21.84** (1.35 to 353.24)	20 per 1.000 [4]	**417 more per 1.000** (7 more to 7045 more) [4]

Imiquimod 5% cream + argon plasma coagulation compared to argon plasma coagulation alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With argon plasma coagulation	With Imiquimod 5% cream + argon plasma coagulation	Relative effect (95% CI)	Risk with argon plasma coagulation	Risk difference with Imiquimod 5% cream + argon plasma coagulation
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25
2. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25
3. Very large confidence interval
4. Due to zero observed events, the anticipated risk in the argon plasma coagulation alone group is based on a correction of 0.5 observed events in the argon plasma coagulation alone group. The calculation of the risk in the combined treatment group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the argon plasma coagulation alone group.

2.11. Electrocautery plus cidofovir 1% gel vs. electrocautery

Table 10: Summary of findings: Electrocautery plus cidofovir 1% gel vs. electrocautery

Electrocautery + Cidofovir 1% gel compared to electrocautery alone											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With electro-cautery	**With Electro-cautery + Cidofovir 1% gel**		**Risk with electro-cautery**	**Risk difference with Electro-cautery + Cidofovir 1% gel**
Short-term complete clearance (after EOT) - External AGW											
48 (1 RCT)	serious [1]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	27/29 (93.1%)	19/19 (100.0%)	**RR 1.06** (0.94 to 1.21)	931 per 1.000	**56 more per 1.000** (56 fewer to 196 more)
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (6m after EOT) - External AGW											
30 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	14/19 (73.7%)	3/11 (27.3%)	**RR 0.37** (0.14 to 1.01)	737 per 1.000	**464 fewer per 1.000** (634 fewer to 7 more)

Electrocautery + Cidofovir 1% gel compared to electrocautery alone											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With electro-cautery	**With Electro-cautery + Cidofovir 1% gel**		**Risk with electro-cautery**	**Risk difference with Electro-cautery + Cidofovir 1% gel**
Long-term recurrence (12m after EOT +/- 2m)											
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events											
No data available											
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of performance and detection bias; unclear risk of selection bias

2. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75

2.12. Electrocautery plus cidofovir 1% gel vs. cidofovir 1% gel

Table 11: Summary of findings: Electrocautery plus cidofovir 1% gel vs. cidofovir 1% gel

Electrocautery + cidofovir 1% gel compared to cidofovir 1% gel alone											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With cidofovir 1% gel	**With electrocautery + cidofovir 1% gel**		**Risk with electrocautery + cidofovir 1% gel**	**Risk difference with Cidofovir 1% gel**
Short-term complete clearance (after EOT) - External AGW											
45 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	20/26 (76.9%)	19/19 (100%)	**RR 1.28** (1.03 to 1.61)	769 per 1.000	**215 more per 1.000** (23 more to 469 more)
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (6m after EOT) - External AGW											

Electrocautery + cidofovir 1% gel compared to cidofovir 1% gel alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With cidofovir 1% gel	With electrocautery + cidofovir 1% gel	Relative effect (95% CI)	Risk with electrocautery + cidofovir 1% gel	Risk difference with Cidofovir 1% gel
28 (1 RCT)	serious [1]	not serious	not serious	serious [3]	none	⨁⨁◯◯ LOW	6/17 (35.3%)	3/11 (27.3%)	**RR 0.77** (0.24 to 2.46)	353 per 1.000	**81 fewer per 1.000** (268 fewer to 515 more)
Long-term recurrence (12m after EOT +/- 2m)											
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events											
No data available											
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration - External AGW											

Electrocautery + cidofovir 1% gel compared to cidofovir 1% gel alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With cidofovir 1% gel**	**With electrocautery + cidofovir 1% gel**	**Relative effect (95% CI)**	**Risk with electrocautery + cidofovir 1% gel**	**Risk difference with Cidofovir 1% gel**
45 (1 RCT)	serious [1]	not serious	not serious	serious [3]	none	⨁⨁◯◯ LOW	11/26 (42.3%)	6/19 (31.6%)	**RR 0.75** (0.34 to 1.66)	423 per 1.000	**106 fewer per 1.000** (279 fewer to 279 more)
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of performance and detection bias; unclear risk of selection bias
2. Confidence interval crosses minimal important difference threshold of 1.25
3. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25

2.13. IFN alpha-2b (les.) plus podophyllin 25% sol. vs. podophyllin 25% sol.

Table 12: Summary of findings: IFN alpha-2b (intralesional) plus podophyllin 25% sol. vs. podophyllin 25% sol.

IFN alpha-2b (intralesional) + podophyllin 25% sol. compared to podophyllin 25% sol. alone											
Quality assessment							**Summary of findings**				
							Study event rates (%)			**Anticipated absolute effects**	
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With podo-phyllin 25% sol.**	**With IFN alpha-2b (intralesional) + podophyllin 25% sol.**	**Relative effect (95% CI)**	**Risk with podophyllin 25% sol.**	**Risk difference with IFN alpha-2b (intralesional) + podophyllin 25% sol.**
Short-term complete clearance (after EOT) - External AGW											
13 (1 study)	-	-	-	-	-	-	0/7 (0.0%)	0/6 (0.0%)	not estimable	not estimable	
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (24w after EOT +/- 16w)											
No data available											
Long-term recurrence (12m after EOT +/- 2m)											
No data available											

IFN alpha-2b (intralesional) + podophyllin 25% sol. compared to podophyllin 25% sol. alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With podo-phyllin 25% sol.	With IFN alpha-2b (intralesional) + podophyllin 25% sol.	Relative effect (95% CI)	Risk with podophyllin 25% sol.	Risk difference with IFN alpha-2b (intralesional) + podophyllin 25% sol.
Quality of life after EOT											
No data available											
Dropouts due to adverse events - External AGW											
109 (1 RCT)	not serious	not serious	not serious	very serious [1]	none	⨁⨁◯◯ LOW	0/56 (0.0%)	2/53 (3.8%)	**RR 5.28** (0.26 to 107.44)	9 per 1.000 [5]	**39 more per 1.000** (7 fewer to 958 more) [5]
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation - External AGW											
108 (1 RCT)	not serious	not serious	not serious	serious [2]	none	⨁⨁⨁◯ MODERATE	19/55 (34.5%)	21/53 (39.6%)	**RR 1.15** (0.70 to 1.88)	345 per 1.000	**52 more per 1.000** (104 fewer to 304 more)
Local AE: erosion / excoriation / ulceration											
No data available											
Influenza-like symptoms											

IFN alpha-2b (intralesional) + podophyllin 25% sol. compared to podophyllin 25% sol. alone											
Quality assessment							**Summary of findings**				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With podo-phyllin 25% sol.	**With IFN alpha-2b (intralesional) + podophyllin 25% sol.**		**Risk with podophyllin 25% sol.**	**Risk difference with IFN alpha-2b (intralesional) + podophyllin 25% sol.**
109 (1 RCT)	serious [3]	not serious	not serious	serious [4]	none	⨁⨁◯◯ LOW	0/56 (0.0%)	49/53 (92.5%)	**RR 104.50** (6.61 to 1652.40)	9 per 1.000 [5]	**932 more per 1.000** (50 more to 14863 more) [5]
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference; **OR:** Odds ratio

1. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25; very large confidence interval
2. Confidence interval crosses line of no effect and minimal important difference threshold of 0.75 and 1.25
3. High risk of performance bias
4. Very large confidence interval
5. Due to zero observed events, the anticipated risk in the podophyllin alone group is based on a correction of 0.5 observed events in the podophyllin alone group. The calculation of the risk in the combined treatment group and its 95% confidence interval is based on the 0.5 corrected assumed risk in the podophyllin alone group.

2.14. IFN alpha-n3 (intralesional) plus electrocautery vs. electrocautery

Table 13: Summary of findings: IFN alpha-n3 (intralesional) plus electrocautery vs. electrocautery

IFN alpha-n3 (intralesional) + electrocautery compared to electrocautery alone												
Quality assessment							**Summary of findings**					
							Study event rates (%)			**Anticipated absolute effects**		
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With electro-cautery**	**With IFN alpha-n3 (intra-lesional) + electro-cautery**	**Relative effect (95% CI)**	**Risk with electro-cautery**	**Risk difference with IFN alpha-n3 (intra-lesional) + electro-cautery**
Short-term complete clearance (4w after EOT +/-4w)											
No data available											
Reduction in disease severity: partial clearance at EOT											
No data available											
Intermediate-term complete clearance (24w after EOT +/-16w)											
No data available											
Long-term complete clearance (12m after EOT +/-2m)											
No data available											
Intermediate-term recurrence (6m after EOT) - Internal and external AGW											
20 (1 RCT)	serious [1]	not serious	not serious	serious [2]	none	⨁⨁◯◯ LOW	3/7 (42.9%)	2/13 (15.4%)	**RR 0.36** (0.08 to 1.67)	429 per 1.000	**274 fewer per 1.000** (394 fewer to 287 more)
Long-term recurrence (12m after EOT +/- 2m)											

IFN alpha-n3 (intralesional) + electrocautery compared to electrocautery alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electro-cautery	With IFN alpha-n3 (intra-lesional) + electro-cautery	Relative effect (95% CI)	Risk with electro-cautery	Risk difference with IFN alpha-n3 (intra-lesional) + electro-cautery
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events											
No data available											
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of selection bias and detection bias
2. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25

2.15. IFN alpha-2b (systemical) plus electrocautery vs. electrocautery

Table 14: Summary of findings: IFN alpha-2b (systemical) plus electrocautery vs. electrocautery

IFN alpha-2b (systemical) + electrocautery compared to electrocautery alone												
Quality assessment							**Summary of findings**					
							Study event rates (%)			**Anticipated absolute effects**		
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**With electro-cautery**	**With IFN alpha-2b (systemical) + electro-cautery**	**Relative effect (95% CI)**	**Risk with electro-cautery**	**Risk difference with IFN alpha-2b (systemical) + electro-cautery**
Short-term complete clearance at EOT - External and internal AGW											
22 (1 observational study)	serious [1]	not serious	not serious	very serious [2]	none	⨁◯◯◯ VERY LOW	0/10 (0.0%)	4/12 (33.3%)	**RR 7.62** (0.46 to 126.40)	50 per 1.000 [5]	**331 more per 1.000** (27 fewer to 6270 more) [5]
Reduction in disease severity: partial or complete clearance (≥50% clearance) at EOT - External and internal AGW											
22 (1 observational study)	serious [1]	not serious	not serious	very serious [3]	none	⨁◯◯◯ VERY LOW	0/10 (0.0%)	8/12 (66.7%)	**RR 14.38** (0.93 to 222.06)	50 per 1.000 [5]	**669 more per 1.000** (4 fewer to 11053 more) [5]
Intermediate-term complete clearance (6m after EOT) - External and internal AGW											
22 (1 observational study)	serious [1]	not serious	not serious	very serious [2]	none	⨁◯◯◯ VERY LOW	0/10 (0.0%)	4/12 (33.3%)	**RR 7.62** (0.46 to 126.40)	50 per 1.000 [5]	**331 more per 1.000** (27 fewer to 6270 more) [5]
Long-term complete clearance (12m after EOT +/-2m)											
No data available											

IFN alpha-2b (systemical) + electrocautery compared to electrocautery alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electro-cautery	With IFN alpha-2b (systemical) + electro-cautery	Relative effect (95% CI)	Risk with electro-cautery	Risk difference with IFN alpha-2b (systemical) + electro-cautery
Intermediate-term recurrence (24w after EOT +/- 16w)											
No data available											
Long-term recurrence (12m after EOT +/- 2m)											
No data available											
Quality of life after EOT											
No data available											
Dropouts due to adverse events - External and internal AGW											
22 (1 observational study)	serious [1]	not serious	not serious	serious [4]	none	⨁◯◯◯ VERY LOW	0/10 (0.0%)	2/12 (16.7%)	**RR 4.23** (0.23 to 79.10)	50 per 1.000 [5]	**162 more per 1.000** (39 fewer to 3905 more) [5]
Pain during treatment and 0-4w after EOT											
No data available											
Local AE: erythema / inflammation / skin irritation											
No data available											
Local AE: erosion / excoriation / ulceration											
No data available											

IFN alpha-2b (systemical) + electrocautery compared to electrocautery alone

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With electro-cautery	With IFN alpha-2b (systemical) + electro-cautery	Relative effect (95% CI)	Risk with electro-cautery	Risk difference with IFN alpha-2b (systemical) + electro-cautery
Progressive disease with respect to grade of dysplasia											
No data available											

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

1. High risk of selection bias, performance bias, detection bias, and reporting bias
2. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25; very large confidence interval
3. Confidence interval crosses line of no effect and minimal important difference threshold of 1.25; very large confidence interval
4. Confidence interval crosses line of no effect and minimal important difference thresholds of 0.75 and 1.25
5. Due to zero observed events, the anticipated risk in the electrocautery group is based on a correction of 0.5 observed events in the electrocautery group. The calculation of the risk in the IFN + electrocautery group is based on the 0.5 corrected assumed risk in the electrocautery group.

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