Adjuvant treatment of anogenital warts with systemic interferon:

A systematic review and meta-analysis

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**Online-Supplement**

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# Abbreviations

CC – complete clearance

GRADE – Grading of Recommendations Assessment, Development and Evaluation

MID – minimal important difference

RCT – randomized controlled trials

SIGN – Scottish Intercollegiate Guidelines Network

# Methods

# Search strategy

The search strategy consisted of three parts:

1. Scottish Intercollegiate Guidelines Network (SIGN) filter for randomized controlled trials (RCTs, lines 1-29).1
2. Identification of the population regarding disease (lines 30-53).
3. The intervention was identified using the term “interferon” and the corresponding MeSH term (lines 54-56).

The three parts were connected with the operator AND (line 57).

Complete search strategy used in MEDLINE

1. Randomized Controlled Trials as Topic/

2. randomized controlled trial/

3. Random Allocation/

4. Double Blind Method/

5. Single Blind Method/

6. clinical trial/

7. clinical trial, phase i.pt.

8. clinical trial, phase ii.pt.

9. clinical trial, phase iii.pt.

10. clinical trial, phase iv.pt.

11. controlled clinical trial.pt.

12. randomized controlled trial.pt.

13. multicenter study.pt.

14. clinical trial.pt.

15. exp Clinical Trials as topic/

16. or/1-15

17. (clinical adj trial$).tw.

18. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

19. PLACEBOS/

20. placebo$.tw.

21. randomly allocated.tw.

22. (allocated adj2 random$).tw.

23. or/17-22

24. 16 or 23

25. case report.tw.

26. letter/

27. historical article/

28. or/25-27

29. 24 not 28

30. exp Papillomavirus infection/

31. HPV.ab,ti.

32. (papillomavirus or "papilloma virus").ab,ti.

33. wart$.ab,ti.

34. or/30-33

35. anogenital.ab,ti.

36. anal.ab,ti.

37. genital.ab,ti.

38. genitoanal.ab,ti.

39. vulva$.ab,ti.

40. perianal.ab,ti.

41. vagina$.ab,ti.

42. (penis or penile).ab,ti.

43. scrotal.ab,ti.

44. mucocutaneous.ab,ti.

45. venereal.ab,ti.

46. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

47. 34 and 46

48. Condylomata Acuminata/

49. "condyloma$ acuminat$".ab,ti.

50. "condyloma$ accuminat$".ab,ti.

51. condyloma$.ab,ti.

52. or/48-51

53. 47 or 52

54. Interferons/

55. interferon$.ab,ti.

56. 54 or 55

57. 29 and 53 and 56

# Data items

Besides the study characteristics (intervention and comparison, patients randomized, treatment duration), the extracted data items included information regarding inclusion/exclusion criteria (total number of warts and wart area, age, gender, immune status), baseline population characteristics (age, gender, total number of warts and wart area, duration of disease, previous treatment, localization of warts), dropouts, adverse events, and results.

# GRADE evaluations

The ‘Grading of Recommendations Assessment, Development and Evaluation’ (GRADE) approach was applied to assess the quality of the evidence on the outcome level.2 The default value of the GRADE quality of the evidence was set on ‘high’ (all data derived from RCTs) which was downgraded to ‘moderate’, ‘low’ or ‘very low’ according to the following five criteria if appropriate.

# Downgrading due to risk of bias

On the study level, the risk of bias was evaluated with the ‘Cochrane Collaboration’s tool for assessing risk of bias in randomized trials’.3 The results of this assessment were then used to determine the risk of bias ratings at the outcome level: The risk of bias of all contributing RCTs was considered and downgrading was conducted if high risk ratings exceeded low risk ratings. However, not all categories of the risk of bias tool were considered equally for all outcomes. For patient-reported outcomes, the aspect of blinding of participants was considered more relevant. For investigator-reported outcomes, we considered the categories of sequence generation, allocation concealment, and blinding of outcome assessment as more relevant.

# Downgrading due to inconsistency

This criterion considered the relation of point estimates and their 95% confidence intervals of the studies contributing results to a pooled estimate of effect, as well as statistical heterogeneity as measured by I².4 Downgrading was performed if the confidence intervals were not or only barely overlapping, and in case I² exceeded 50%. If only one RCT contributed data to an outcome, downgrading concerning inconsistency was not performed.

# Downgrading due to indirectness

This criterion considered the population, intervention, comparison and outcomes of the included studies and compared them to PICO question of the systematic review. The results were downgraded whenever a significant deviation was noted.5 Due to the exact definition of the eligibility criteria along the PICO question of the systematic review, downgrading for indirectness was usually not necessary.

# Downgrading due to imprecision

Downgrading due to an imprecise result was conducted under two conditions:

1. The confidence interval crossed a predefined threshold of the minimal important difference (MID).6 The MID threshold was defined as 0.75 and 1.25 (for dichotomous outcomes).
2. The confidence interval was considered very large.7 The values of 0.01 and 100 were defined as thresholds for this condition.

If both criteria were met, two steps of downgrading were performed.

# Downgrading due to publication bias

No trial register searches were performed. Funnel plots (calculated with the Review Manager 5.3.58) were used to assess the risk of publication bias in case at least ten trials contributed data for one outcome. If this threshold was not reached, publication bias was rated as “undetected”.

# Results

# Reasons for the exclusion of studies

Table 1 gives an overview of reasons for the exclusion of studies during the full-text evaluation.

Table 1: Reasons for exclusion of studies during the full-text evaluation

|  |  |
| --- | --- |
| **Study** | **Reasons for exclusion** |
| Alfonso Trujillo et al. 20149 | language: Spanish |
| Aste et al. 199510 | cohort study |
| Bart, B.J. 198811 | only abstract available |
| Bonnez et al. 199512 | data reported elsewhere13 |
| Cardamakis et al. 199714 | not randomized |
| Erpenbach et al. 198915 | cohort study |
| Facchini et al. 199616 | language: Italian |
| Fleshner et. al. 199417 | IFN not applied systemically |
| Gross et al. 199818 | IFN not applied systemically |
| Gross et al. 199619 | not randomized |
| Handley et al. 199220 | only abstract available |
| Klutke et al. 199521 | IFN not applied systemically |
| Martius et al. 199322 | cohort study |
| Mendelson et al. 199323 | data reported elsewhere24 |
| Nieminen et al. 199425 | high proportion of IEN within the population |
| Reid et al. 199226 | no relevant outcome reported |
| Relakis et al. 1996a27 | not randomized |
| Relakis et al. 1996b28 | not randomized |
| Stellato et al. 1997a29 | data reported elsewhere25; High proportion of IEN within the population |
| Stellato et al. 1997b30 | data reported elsewhere25; High proportion of IEN within the population |
| Wang et al. 199831 | language: Chinese |
| Wei et al 200132 | language: Chinese |

# Risk of bias

Regarding sequence generation, eight trials (67%) were rated to be at unclear risk of bias, whereas four studies (33%) reported sufficient information for a low risk judgement. A single trial (8%) was evaluated to be at high risk of bias concerning allocation concealment; the eleven remaining trials (92%) were rated to hold an unclear risk of bias. For the blinding of participants and personnel, both low and high-risk ratings were seen in five trials (each 42%); in 2 studies, this criterion was judged to be at an unclear risk. A single trial (8%) exhibited a low risk regarding the blinding of outcome assessment. Six (50%) and five (42%) studies showed an unclear or high-risk of bias due to no or unclear methods used to blind the outcome assessment, respectively. Concerning the criterion of incomplete outcome data, two studies (17%) were rated to be at low risk, and another two trials at unclear risk of bias. For this criterion, the highest percentage of high-risk-ratings (67%, 8 trials) was seen. Selective reporting was rated with an unclear risk in 9 trials (75%), while 3 studies were judged to hold a high risk of bias. A similar picture emerged for the criterion of other sources of bias: ten trials (83%) were rated to be at unclear risk of bias while the remaining two studies (17%) were rated to exhibit a high risk of bias.

The results regarding the risk of bias at the study level are summarized in Figure 1 (risk of bias graph) and presented in the original publication (Figure 2, risk of bias summary) with evaluations for each included study.

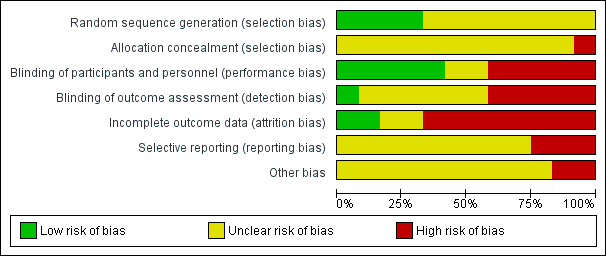


Figure 1: Risk of bias graph: Distribution of risk of bias judgements across all included studies.

# Additional information

# Bonnez 1995

The study by Bonnez et al. 199513 presented efficacy data in percentage (Figure 1, p. 1084) but did not report the sample size for each single group during the period of assessment. Therefore, the calculation of the required absolute data for a meta-analysis was not possible. The trial compared high dose preparations of alpha-, beta-, gamma-IFN and placebo in combination with cryotherapy and reported no significant differences between these groups (page 1084).

# Roemisch 1992

The trial by Roemisch et al. 199233 did not state the distribution of its participants (N=24) to the two study groups. We assumed a 1:1 randomization ratio.

# Summary of findings tables

# Adjuvant alpha-IFN vs. placebo or no treatment

Table 2: Summary of findings: Adjuvant alpha-IFN vs. placebo or no treatment

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant alpha-IFN compared to placebo for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant alpha-IFN  **Comparison**: adjuvant placebo/ no treatment | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with placebo** | **Risk with alpha-IFN** |
| Complete clearance at 4w (+/- 4w) after EOT | 574 per 1.000 | **557 per 1.000** (494 to 626) | **RR 0.97** (0.86 to 1.09) | 634 (5 RCTs) | ⨁⨁⨁◯ MODERATE 1 |  |
| Complete clearance at 4w (+/- 4w) after EOT - High dose (3x per week) | 559 per 1.000 | **542 per 1.000** (475 to 615) | **RR 0.97** (0.85 to 1.10) | 508 (5 RCTs) | ⨁⨁⨁◯ MODERATE 1 |  |
| Complete clearance at 4w (+/- 4w) after EOT - Low dose (3x per week) | 659 per 1.000 | **632 per 1.000** (481 to 836) | **RR 0.96** (0.73 to 1.27) | 126 (1 RCT) | ⨁⨁◯◯ LOW 2,3 |  |
| Complete clearance at 16w (+/- 8w) after EOT | 257 per 1.000 | **419 per 1.000** (198 to 890) | **RR 1.63** (0.77 to 3.46) | 150 (3 RCTs) | ⨁◯◯◯ VERY LOW 4,5,6 |  |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (3x per week) | 278 per 1.000 | **356 per 1.000** (153 to 825) | **RR 1.28** (0.55 to 2.97) | 115 (2 RCTs) | ⨁◯◯◯ VERY LOW 1,3,7 |  |
| Complete clearance at 16w (+/- 8w) after EOT - Low dose (daily application) | 188 per 1.000 | **579 per 1.000** (195 to 1.000) | **RR 3.09** (1.04 to 9.18) | 35 (1 RCT) | ⨁⨁◯◯ LOW 6,8 |  |
| Drop outs due to adverse events - High dose (3x per week) | 9 per 1.000 | **24 per 1.000** (6 to 95) | **RR 2.57** (0.65 to 10.09) | 432 (5 RCTs) | ⨁⨁⨁◯ MODERATE 3 |  |
| Fever or flu-like symptoms - High dose (3x per week) | 99 per 1.000 | **341 per 1.000** (191 to 607) | **RR 3.45** (1.93 to 6.15) | 332 (4 RCTs) | ⨁⨁⨁⨁ HIGH |  |
| Headache - High dose (3x per week) | 259 per 1.000 | **436 per 1.000** (251 to 754) | **RR 1.68** (0.97 to 2.91) | 332 (4 RCTs) | ⨁⨁◯◯ LOW 6,9 |  |
| Fatigue - High dose (3x per week) | 204 per 1.000 | **230 per 1.000** (165 to 320) | **RR 1.13** (0.81 to 1.57) | 332 (4 RCTs) | ⨁⨁⨁◯ MODERATE 6 |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT | 0 per 1.000 | **0 per 1.000** (0 to 0) | not estimable | (0 studies) | - | Not pooled due to statistical heterogeneity. |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT - High dose (3x per week) | 222 per 1.000 | **382 per 1.000** (187 to 789) | **RR 1.72** (0.84 to 3.55) | 72 (2 RCTs) | ⨁⨁⨁◯ MODERATE 6 |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT - Low dose (daily application) | 813 per 1.000 | **423 per 1.000** (236 to 748) | **RR 0.52** (0.29 to 0.92) | 35 (1 RCT) | ⨁⨁◯◯ LOW 8,10 |  |
| Complete clearance at 12m (+/- 6m) after EOT | 313 per 1.000 | **323 per 1.000** (248 to 420) | **RR 1.03** (0.79 to 1.34) | 492 (3 RCTs) | ⨁⨁⨁◯ MODERATE 6 |  |
| Complete clearance at 12m (+/- 6m) after EOT - High dose (3x per week) | 300 per 1.000 | **318 per 1.000** (234 to 432) | **RR 1.06** (0.78 to 1.44) | 366 (3 RCTs) | ⨁⨁⨁◯ MODERATE 6 |  |
| Complete clearance at 12m (+/- 6m) after EOT - Low dose (3x per week) | 366 per 1.000 | **351 per 1.000** (216 to 578) | **RR 0.96** (0.59 to 1.58) | 126 (1 RCT) | ⨁⨁⨁◯ MODERATE 3 |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) | 591 per 1.000 | **591 per 1.000** (502 to 703) | **RR 1.00** (0.85 to 1.19) | 373 (3 RCTs) | ⨁⨁⨁⨁ HIGH |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) - High dose (3x per week) | 622 per 1.000 | **622 per 1.000** (523 to 746) | **RR 1.00** (0.84 to 1.20) | 292 (3 RCTs) | ⨁⨁⨁⨁ HIGH |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) - Low dose (3x per week) | 444 per 1.000 | **444 per 1.000** (267 to 747) | **RR 1.00** (0.60 to 1.68) | 81 (1 RCT) | ⨁⨁⨁◯ MODERATE 3 |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. high risk of attrition bias; unclear risk of selection bias
2. high risk of attrition and reporting bias; unclear risk of selection bias
3. confidence interval crosses the MID thresholds of 0.75 and 1.25
4. high risk of attrition and detection bias; unclear risk of selection bias
5. I²=52%; different dosing schedules
6. confidence interval crosses the MID threshold of 1.25
7. I²=52%
8. high risk of bias in various categories
9. I²=55%
10. confidence interval crosses the MID threshold of 0.75

# Adjuvant beta-IFN vs. placebo or no treatment

Table 4: Summary of findings: Adjuvant beta-IFN vs. placebo or no treatment

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant beta-IFN compared to placebo for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant beta-IFN  **Comparison**: adjuvant placebo/ no treatment | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with placebo** | **Risk with beta-IFN** |
| Complete clearance at 4w (+/- 4w) after EOT - High dose (daily application) | 394 per 1.000 | **347 per 1.000** (177 to 682) | **RR 0.88** (0.45 to 1.73) | 59 (1 RCT) | ⨁⨁◯◯ LOW 1,2 |  |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (daily application) | 727 per 1.000 | **887 per 1.000** (691 to 1.000) | **RR 1.22** (0.95 to 1.56) | 59 (1 RCT) | ⨁⨁◯◯ LOW 1,3 |  |
| Drop outs due to adverse events - High dose (3x per week) | 0 per 1.000 | **0 per 1.000** (0 to 0) | not estimable | 78 (1 study) | - | zero events occurred |
| Fever or flu-like symptoms - High dose (3x per week) | 205 per 1.000 | **226 per 1.000** (96 to 523) | **RR 1.10** (0.47 to 2.55) | 79 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Headache - High dose (3x per week) | 538 per 1.000 | **474 per 1.000** (307 to 732) | **RR 0.88** (0.57 to 1.36) | 79 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Fatigue - High dose (3x per week) | 564 per 1.000 | **547 per 1.000** (372 to 812) | **RR 0.97** (0.66 to 1.44) | 79 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 12m (+/- 6m) after EOT |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) |  |  | no data available | (0 studies) | - |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. high risk of performance and detection bias
2. Confidence interval crosses the MID threshold of 0.75 and 1.25
3. Confidence interval crosses the MID threshold of 1.25

# Adjuvant gamma-IFN vs. placebo or no treatment

Table 6: Summary of findings: Adjuvant gamma-IFN vs. placebo or no treatment

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant gamma-IFN compared to placebo for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant gamma-IFN  **Comparison**: adjuvant placebo/ no treatment | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with placebo** | **Risk with gamma-IFN** |
| Complete clearance at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (3x per week) |  |  | no data available | (0 studies) | - |  |
| Drop outs due to adverse events | not pooled | not pooled | not pooled | 95 (2 studies) | - | zero events occurred |
| Drop outs due to adverse events - High dose (3x per week) | 0 per 1.000 | **0 per 1.000** (0 to 0) | not estimable | 75 (1 study) | - | zero events occurred |
| Drop outs due to adverse events - Low dose (daily application) | 0 per 1.000 | **0 per 1.000** (0 to 0) | not estimable | 20 (1 study) | - | zero events occurred |
| Fever or flu-like symptoms - High dose (3x per week) | 205 per 1.000 | **459 per 1.000** (226 to 933) | **RR 2.24** (1.10 to 4.55) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Headache - High dose (3x per week) | 538 per 1.000 | **894 per 1.000** (652 to 1.000) | **RR 1.66** (1.21 to 2.26) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Fatigue - High dose (3x per week) | 564 per 1.000 | **756 per 1.000** (542 to 1.000) | **RR 1.34** (0.96 to 1.87) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT - Low dose (daily application) | 500 per 1.000 | **600 per 1.000** (270 to 1.000) | **RR 1.20** (0.54 to 2.67) | 20 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Complete clearance at 12m (+/- 6m) after EOT - Low dose (daily application) | 400 per 1.000 | **500 per 1.000** (188 to 1.000) | **RR 1.25** (0.47 to 3.33) | 20 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) - Low dose (daily application) | 500 per 1.000 | **500 per 1.000** (195 to 1.000) | **RR 1.00** (0.39 to 2.53) | 18 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. Confidence interval crosses the MID threshold of 1.25
2. Confidence interval crosses the MID thresholds of 0.75 and 1.25

# Adjuvant alpha-IFN high dose vs. low dose

Table 3: Summary of findings: Adjuvant alpha-IFN high dose vs. low dose

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant alpha-IFN / high dose compared to low dose for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant alpha-IFN / high dose  **Comparison**: adjuvant alpha-IFN / low dose | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with low dose (3x per week)** | **Risk with alpha-IFN / high dose (3x per week)** |
| Complete clearance at 4w (+/- 4w) after EOT | 635 per 1.000 | **699 per 1.000** (565 to 864) | **RR 1.10** (0.89 to 1.36) | 168 (1 RCT) | ⨁⨁◯◯ LOW 1,2 |  |
| Complete clearance at 16w (+/- 8w) after EOT |  |  | no data available | (0 studies) | - |  |
| Drop outs due to adverse events | 83 per 1.000 | **167 per 1.000** (17 to 1.000) | **RR 2.00** (0.21 to 19.23) | 24 (1 RCT) | ⨁⨁◯◯ LOW 3,4 |  |
| Fever or flu-like symptoms |  |  | no data available | (0 studies) | - |  |
| Headache |  |  | no data available | (0 studies) | - |  |
| Fatigue |  |  | no data available | (0 studies) | - |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 12m (+/- 6m) after EOT | 381 per 1.000 | **423 per 1.000** (301 to 599) | **RR 1.11** (0.79 to 1.57) | 192 (2 RCTs) | ⨁⨁◯◯ LOW 1,2 |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) | 403 per 1.000 | **387 per 1.000** (222 to 677) | **RR 0.96** (0.55 to 1.68) | 129 (2 RCTs) | ⨁⨁◯◯ LOW 1,4 |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. high risk of attrition bias; unclear risk of selection bias
2. Confidence interval crosses the MID threshold of 1.25
3. high risk of performance, detection and attrition bias
4. Confidence interval crosses the MID thresholds of 0.75 and 1.25

# Adjuvant beta-IFN very high dose vs. high dose

Table 5: Summary of findings: Adjuvant beta-IFN very high dose vs. high dose

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant beta-IFN / very high dose compared to high dose for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: beta-IFN / very high dose  **Comparison**: beta-IFN / high dose | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with high dose (3x per week)** | **Risk with beta-IFN / very high dose (3x per week)** |
| Complete clearance at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT | 440 per 1.000 | **440 per 1.000** (238 to 823) | **RR 1.00** (0.54 to 1.87) | 50 (1 RCT) | ⨁⨁◯◯ LOW 1,2 |  |
| Drop outs due to adverse events | 0 per 1.000 | **0 per 1.000** (0 to 0) | **RR 3.00** (0.13 to 70.30) | 50 (1 RCT) | ⨁⨁◯◯ LOW 2,3 |  |
| Fever or flu-like symptoms | 440 per 1.000 | **722 per 1.000** (436 to 1.000) | **RR 1.64** (0.99 to 2.71) | 50 (1 RCT) | ⨁⨁◯◯ LOW 3,4 |  |
| Headache | 760 per 1.000 | **920 per 1.000** (714 to 1.000) | **RR 1.21** (0.94 to 1.55) | 50 (1 RCT) | ⨁⨁◯◯ LOW 3,4 |  |
| Fatigue |  |  | no data available | (0 studies) | - |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 12m (+/- 6m) after EOT |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) |  |  | no data available | (0 studies) | - |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. high risk of attrition bias; unclear risk of selection bias; data derived from figure
2. Confidence interval crosses the MID thresholds of 0.75 and 1.25
3. high risk of attrition bias; unclear risk of selection bias
4. Confidence interval crosses the MID threshold of 1.25

# Adjuvant alpha-IFN vs. beta-IFN

Table 7: Summary of findings: Adjuvant alpha-IFN vs. beta-IFN

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant alpha-IFN compared to beta-IFN for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant alpha-IFN  **Comparison**: adjuvant beta-IFN | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with beta-IFN** | **Risk with alpha-IFN** |
| Complete clearance at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (3x per week) |  |  | no data available | (0 studies) | - |  |
| Drop outs due to adverse events - High dose (3x per week) | 0 per 1.000 | **0 per 1.000** (0 to 0) | **RR 3.32** (0.14 to 79.11) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Fever or flu-like symptoms - High dose (3x per week) | 225 per 1.000 | **473 per 1.000** (241 to 925) | **RR 2.10** (1.07 to 4.11) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Headache - High dose (3x per week) | 475 per 1.000 | **665 per 1.000** (446 to 993) | **RR 1.40** (0.94 to 2.09) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Fatigue - High dose (3x per week) | 550 per 1.000 | **611 per 1.000** (418 to 897) | **RR 1.11** (0.76 to 1.63) | 76 (1 RCT) | ⨁⨁⨁◯ MODERATE 2 |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 12m (+/- 6m) after EOT |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) |  |  | no data available | (0 studies) | - |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. Confidence interval crosses the MID thresholds of 0.75 and 1.25
2. Confidence interval crosses the MID threshold of 1.25

# Adjuvant alpha-IFN vs. gamma-IFN

Table 8: Summary of findings: Adjuvant alpha-IFN vs. gamma-IFN

| **Summary of findings:** | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant alpha-IFN compared to gamma-IFN for anogenital warts** | | | | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant alpha-IFN  **Comparison**: adjuvant gamma-IFN | | | | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | | Quality of the evidence (GRADE) | | Comments | |
| **Risk with gamma-IFN** | **Risk with alpha-IFN** |  | |  | |  | |  | |
| Complete clearance at 4w (+/- 4w) after EOT |  |  | no data available | | (0 studies) | | - | |  | |
| Complete clearance at 16w (+/- 8w) after EOT |  |  | no data available | | (0 studies) | | - | |  | |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (3x per week) |  |  | no data available | | (0 studies) | | - | |  | |
| Drop outs due to adverse events - High dose (3x per week) | 0 per 1.000 | **0 per 1.000** (0 to 0) | **RR 3.08** (0.13 to 73.24) | | 73 (1 RCT) | | ⨁⨁⨁◯ MODERATE 1 | |  | |
| Fever or flu-like symptoms - High dose (3x per week) | 459 per 1.000 | **473 per 1.000** (289 to 772) | **RR 1.03** (0.63 to 1.68) | | 73 (1 RCT) | | ⨁⨁⨁◯ MODERATE 1 | |  | |
| Headache - High dose (3x per week) | 892 per 1.000 | **669 per 1.000** (517 to 865) | **RR 0.75** (0.58 to 0.97) | | 73 (1 RCT) | | ⨁⨁⨁◯ MODERATE 2 | |  | |
| Fatigue - High dose (3x per week) | 757 per 1.000 | **613 per 1.000** (446 to 840) | **RR 0.81** (0.59 to 1.11) | | 73 (1 RCT) | | ⨁⨁⨁◯ MODERATE 2 | |  | |
| Quality of life |  |  | no data available | | (0 studies) | | - | |  | |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | | (0 studies) | | - | |  | |
| Complete clearance at 12m (+/- 6m) after EOT |  |  | no data available | | (0 studies) | | - | |  | |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) |  |  | no data available | | (0 studies) | | - | |  | |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | | | | |

1. Confidence interval crosses the MID thresholds of 0.75 and 1.25
2. Confidence interval crosses the MID threshold of 0.75

# Adjuvant beta-IFN vs. gamma-IFN

Table 9: Summary of findings: Adjuvant beta-IFN vs. gamma-IFN

| **Summary of findings:** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Adjuvant beta-IFN compared to gamma-IFN for anogenital warts** | | | | | | |
| **Patient or population**: external warts in immunocompetent adults  **Intervention**: adjuvant beta-IFN  **Comparison**: adjuvant gamma-IFN | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with gamma-IFN** | **Risk with beta-IFN** |
| Complete clearance at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 16w (+/- 8w) after EOT - High dose (3x per week) |  |  | no data available | (0 studies) | - |  |
| Drop outs due to adverse events - High dose (3x per week) | 0 per 1.000 | **0 per 1.000** (0 to 0) | not estimable | 77 (1 study) | - | zero events occurred |
| Fever or flu-like symptoms - High dose (3x per week) | 459 per 1.000 | **225 per 1.000** (115 to 441) | **RR 0.49** (0.25 to 0.96) | 77 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Headache - High dose (3x per week) | 892 per 1.000 | **473 per 1.000** (339 to 669) | **RR 0.53** (0.38 to 0.75) | 77 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Fatigue - High dose (3x per week) | 757 per 1.000 | **552 per 1.000** (394 to 772) | **RR 0.73** (0.52 to 1.02) | 77 (1 RCT) | ⨁⨁⨁◯ MODERATE 1 |  |
| Quality of life |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 16w (+/- 8w) after EOT in pts. who had CC at 4w (+/- 4w) after EOT |  |  | no data available | (0 studies) | - |  |
| Complete clearance at 12m (+/- 6m) after EOT |  |  | no data available | (0 studies) | - |  |
| Recurrence of lesions at 12m (+/- 6m) after EOT in pts. who had CC at 4w (+/- 4w) |  |  | no data available | (0 studies) | - |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference | | | | | | |
| **GRADE Working Group grades of evidence** **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

1. Confidence interval crosses the MID threshold of 0.75

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