South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: INTERFERON FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 24 November 2020

NOTE: This rapid review will be updated when the results from the WHO SOLIDARITY trial are available in peer-review format.

Key findings

- Treatment for hospitalised patients with COVID-19 is urgently needed and several potential medicines are being evaluated.
- We conducted a rapid review of available clinical evidence about the use of interferons with or without other medicines for hospitalised patients with COVID-19. The last search was conducted on 27 July 2020.
- We identified one randomised controlled trial with 127 participants comparing interferon β-1b, ribavirin and lopinavir/ritonavir, with lopinavir/ ritonavir in hospitalised adult patients with mild disease that provided low certainty evidence that there may be a shorter hospital stay and faster time to viral clearance in the arm that received interferon β-1b and ribavirin in addition to lopinavir/ritonavir.
- We identified one open label randomised controlled trial with 92 participants comparing subcutaneous interferon β-1a in addition to standard of care (hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir) to standard of care alone, in hospitalised patients with severe disease. We assessed this trial as having a serious risk of bias and overall very low certainty evidence. On intention-to-treat analysis, interferon β-1a did not confer a 28-day mortality benefit (12 vs 17 deaths). Mechanical ventilation was 3 days longer, and there were more adverse effects, in the interferon arm. Interferon β-1a did not shorten duration of hospitalisation or ICU admission.
- We did not identify any reports on the use of interferons in children with COVID-19 and their use is discouraged outside of a clinical trial setting.
- There is currently insufficient evidence to support inclusion of interferons in treatment guidelines for COVID-19 in South Africa until further evaluations are conducted or reported.
- Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Recommendation: We recommend against the use of interferon for the treatment of COVID-19 in hospitalised patients, but eligible patients may be considered in the context of an approved clinical trial.
Rationale: The evidence of efficacy and safety is very uncertain at this point, and cost is a consideration.
Level of Evidence: RCTs of very low quality

(Refer to appendix 3 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Effective therapeutic options to manage hospitalised patients with COVID-19 cases need to be urgently identified. Type 1 interferons, have been suggested as a possible treatment for COVID-19 patients. Type 1 interferons are part of human cellular defences against viral infections. Type 1 interferons mediate suppression of viral replication; they suppress messenger RNA translation and protein synthesis. Interferons also induce changes within cells to make it more likely that the adaptive immune response can recognise infected cells. These mechanisms are also required for normal functioning of cells, which means that interferons have the potential to cause harm by interfering with normal cellular function.

Interferons have previously been investigated as treatment for other coronavirus infections. Use of recombinant interferons in combination with ribavirin was explored in MERS-CoV, with little evidence for efficacy (Kain 2020; https://www.cdc.gov/coronavirus/mers/index.html). There was also no clear evidence for efficacy in treatment of SARS-CoV (Stockman 2006).

There are several reports from observational studies about use of interferons, some of which were described in our first rapid review report (Wei 2020, Wan 2020, Jiu 2020, Jun 2020, Pereda 2020). Observational cohort studies are subject to bias and confounding. Methodological limitations, including prognostically important differences in baseline characteristics between groups make it difficult to reach robust conclusions about efficacy and safety. As randomised trials of interferons have now been completed, we have restricted this update of the rapid review to findings of randomised trials.

QUESTION: Should interferons be used for managing COVID-19?

METHODS

Based on an *a priori* planned rapid review method, we conducted an update to the previous rapid review (29 March 2020) including systematic searching of four electronic databases: PubMed (18 May 2020), Epistemonikos, Cochrane COVID study register and COVID Living Reviews database (www.covid-nma.com) on 22 May 2020. An updated search of the COVID Living Reviews database on 27 July 2020 found no additional studies. Screening of records and data extraction was conducted in duplicate (KC, TK). Relevant records were extracted in a narrative table of results. The Living reviews found on the www.covid-nma.com site follow a pre-specified protocol including duplicate extraction, appraisal using the Cochrane Risk of Bias 2.0 tool and assessment of the overall quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to understand the impact of methodological issues, imprecision, heterogeneity, applicability or directness of the trial to the question, on the overall certainty of the evidence. No meta-analysis was done as the interventions in the two included trials were too different to combine (different interferons were used, and co-medications differed). In one of the included studies, the investigators presented only a per protocol analysis. We performed an intention-to-treat (ITT) analysis for the categorical outcome's "death" and "adverse effects" using Revman 5.4 software. For the ITT analysis of the mortality outcome, we included deaths that occurred after at least one dose of interferon was administered, as reported in the CONSORT diagramme (Davoudi-Monfared). To ensure the imputation done as part of the ITT did not bias the results, we also conducted a sensitivity analysis for the outcomes death and adverse effects (appendix 2).

Eligibility criteria for review

Population: Patients hospitalised with confirmed COVID-19, no age restriction.

Intervention: Type 1 interferon/s either alone or in combination with another medicine. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to oxygen support; duration of ICU stay; duration of oxygen support; adverse events, adverse reactions.

Study designs: Randomised controlled trials, and systematic reviews of randomised controlled trials.

RESULTS

Search results

Our search identified 199 records, 28 duplicates were removed and two reviewers screened 171 records, identifying one eligible trial (Hung 2020). We identified a second trial, published as a non-peer reviewed pre-print on 30 May 2020, which was subsequently accepted and published online on 13 July 2020 (Davoudi-Monfared 2020). A search on 27 July 2020 on www.covid-nma.com found no additional trials.

Both trials are included in the COVID Living Reviews database on the www.covid-nma.com website. We have included the forest plots from the review for Hung *et a*l. below. We generated forest plots for Davoudi-Monfared *et al*. and performed an intention-to-treat (ITT) analysis for death and adverse effects

Table 1 reports the main characteristics and outcomes of the included clinical trials. **Table 2** and **3** are Summary of Findings tables and GRADE assessments for the Hung *et al*. and Davoudi-Monfared *et al*. trials, respectively. **Table 4** reports observational studies previously reported in the rapid review of 29 March 2020. **Table 5** reports the planned ongoing trials as found on the COVID Living Reviews website as of 11 June 2020.

Included trials

1. Lopinavir/ritonavir, ribavirin and interferon β-1b compared to lopinavir/ ritonavir alone

- Hung *et al*. was a multi-centre randomised controlled trial conducted in Hong Kong (Hung 2020) in patients with confirmed SARS-COV2 infection with mild infection based on NEWS2 and SOFA scores (see Table 1).
- The trial included 127 participants and evaluated lopinavir/ritonavir, ribavirin and interferon β-1b (n = 86, of which 52 received interferon β-1b) compared to lopinavir/ ritonavir alone (n = 41).
- For those recruited and treated between days 7 and 14, the interferon β-1b injection was omitted because of concern regarding pro-inflammatory effects.
- Appraisal of the study using Cochrane Risk of Bias tool 2.0 found low risk of bias for the trial conduct, but it should be noted that the lack of blinding may have resulted in biased assessment and reporting of subjective outcomes. Based on the GRADE assessment, there is generally low certainty evidence due to the small sample size and low event rates resulting in imprecision, as well as indirectness due to a single trial in one setting that may not be generalisable to other settings.

Outcomes of interest

i. Mortality was reported as an outcome, but there were no deaths by 7 days or by 28 days.
ii. Duration of hospitalization: a 5.5 day shorter median hospital stay in the intervention group compared to the control group (9 days [7.0–13.0] vs 14.5 days [9.3 – 16.0]; HR 2.72 [1.2–6.13], p=0.016) was reported; low certainty evidence due to single study from one setting and small sample size (imprecision).
iii. Duration of viraemia: time to RT-PCR negativity was 4 fold more rapid in the intervention group (median 7 days [IQR 5–11]) compared to the control group (12 days [IQR 8–15]; Hazard Ratio (HR) 4·37 [95% CI 1·86–10·24]); low certainty evidence due to single study from one setting and small sample size and very wide confidence interval (CI) (imprecision) (Figure 1).
iv. Duration of ICU stay: not reported
v. Duration of respiratory support: not reported
vi. Adverse reactions day 14 - 28: there were 41 adverse events in the intervention group compared to 20 in the control group (Risk ratio 0.96; 95% CI 0.67 – 1.43), equivalent to 10 more adverse events per 1000 people exposed to the intervention treatment. There is low certainty evidence that there is probably no difference in adverse events between groups (Figure 2).
vii. Serious adverse events day 14 – 28: there was one serious adverse event in the intervention arm and none in the control arm (RR 0.16; 95% CI 0.01 – 3.87); very low certainty evidence due to low numbers of events, small sample size (Figure 3).

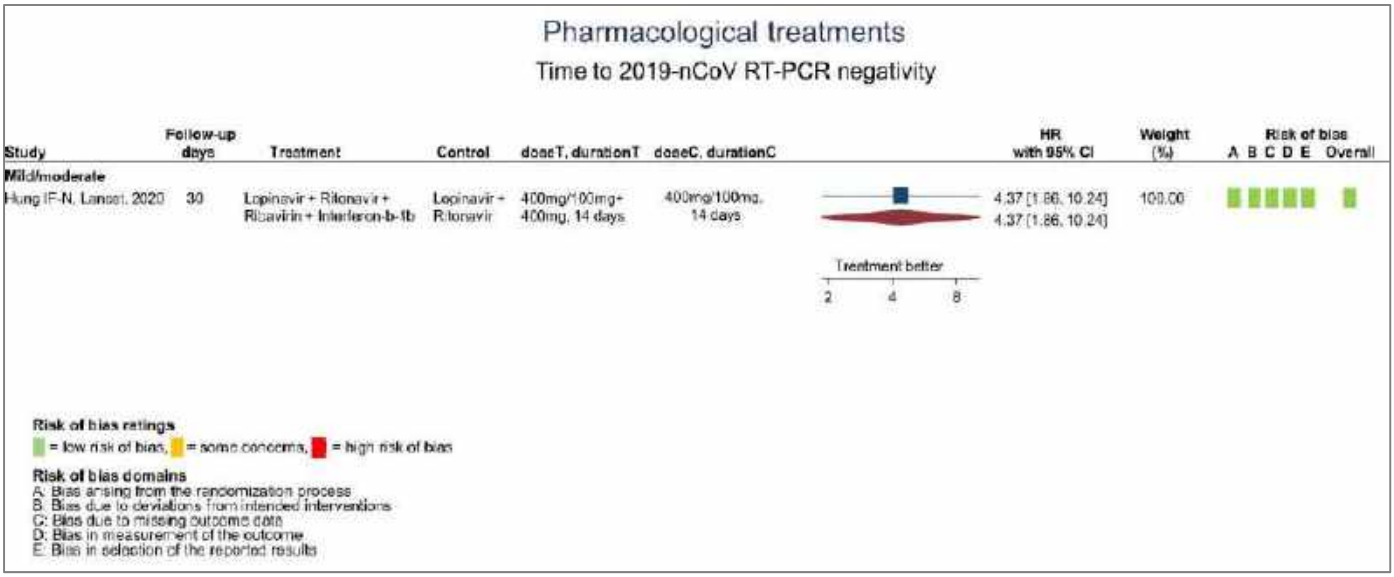

Figure 1. Forest plot of time to RT PCR SARS-COV2 negativity (Hung 2020 trial)

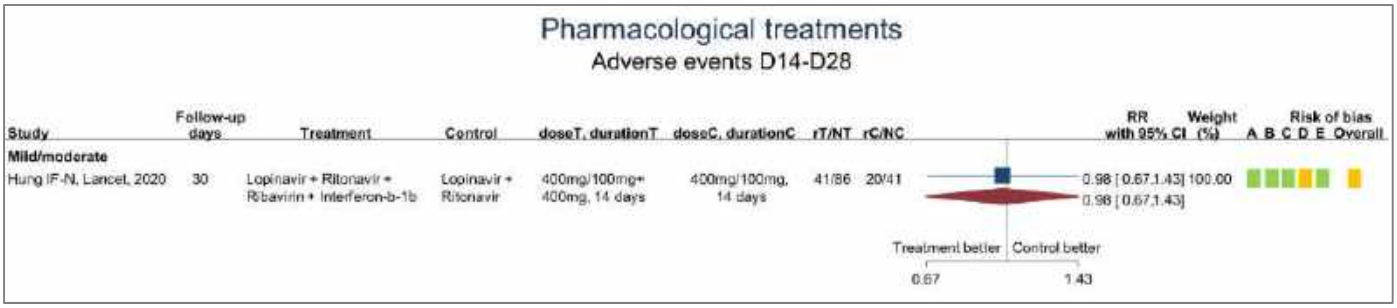

Figure 2. Forest plot of adverse events day 14 – 28 (Hung 2020 trial)

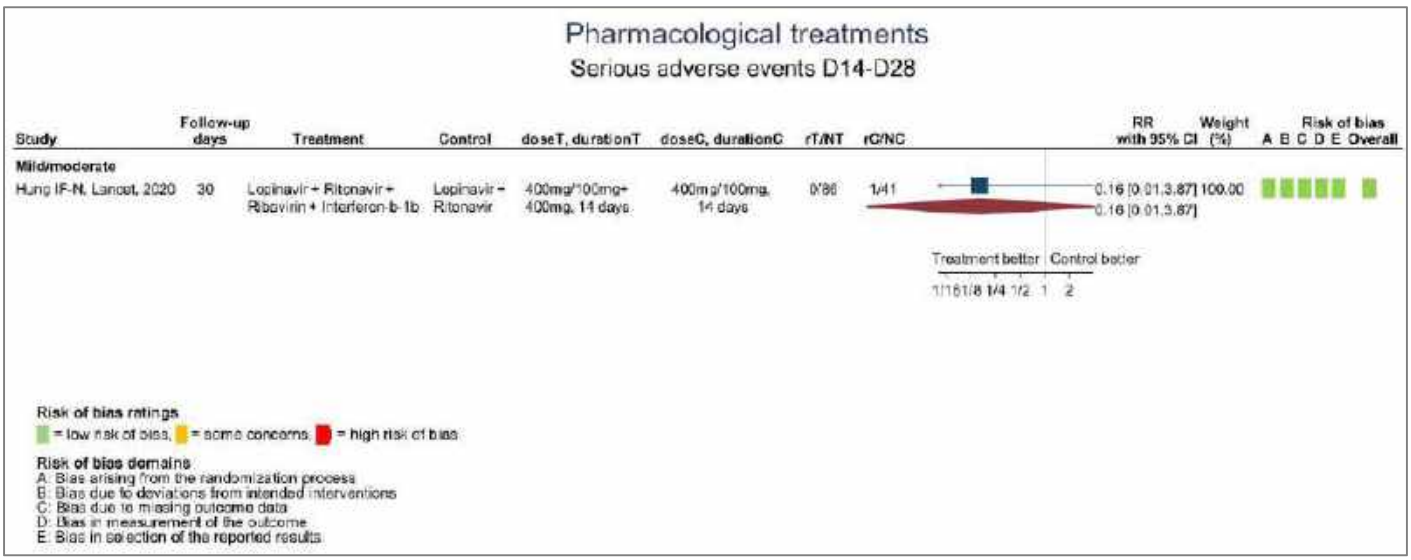

Figure 3. Forest plot of serious adverse events day 14 – 28 (Hung 2020 trial)

2. Interferon β-1a plus standard of care compared to standard of care

- Davoudi-Monfared *et al*. was a randomised controlled trial conducted in hospitalised patients with severe COVID-19 in Tehran, Iran (see Table 1), in which 77% of participants had co-morbidities.
- Ninety-two participants were randomised to two groups: subcutaneous interferon β-1a (46 patients) plus standard of care compared to standard of care alone (46 patients). Standard of care included treatment with hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir.
- Four patients in the IFN group died before the third IFN dose and 7 dropped out of the control group to join another trial. Outcomes in the control group participants who dropped out were not reported. The investigators presented the per-protocol analysis including only 81 participants.
- The trial was appraised as having high risk of bias due to poor reporting of the outcome data, in particular, excluding participants who had been randomised and had died from the analysis. There was also no blinding and poor reporting on randomisation and allocation concealment. The certainty of the evidence, as assessed using GRADE, was very low due to these very serious methodological issues along with the small sample size and low event rates resulting in imprecision, and also indirect evidence (that is, evidence from one trial in one setting that may not be generalisable to other settings).
- We have conducted an intention-to-treat (ITT) analysis, including all randomised participants, for the outcomes of mortality and adverse effects.
    - For the mortality ITT we included the 4 deaths in the interferon group that were included in the CONSORT diagram. As no deaths were reported on the CONSORT for the control participants that "dropped out", we assumed that these 7 participants did not die.
    - For the ITT analysis of adverse effects, we included all 92 participants in the denominator. No adverse effects were described for the 11 participants excluded from the per-protocol analysis presented in the publication; the ITT analysis may therefore underestimate adverse effects.

<u>Outcomes of interest</u>

i. Mortality on day 28: twelve deaths occurred in the IFN group compared to 17 in the control group (Risk Ratio 0.71; 95% CI 0.38 - 1.31); very low certainty evidence (Figure 4).

ii. Duration of hospitalization: the mean hospital duration was reported to be 2.6 days longer in the IFN group compared to control group (95% CI -0.92 - 6.02); very low certainty evidence (Figure 5)

iii. Duration of viraemia: not reported.

iv. Duration of ICU stay: the mean ICU stay was reported to be 0.8 days longer in the IFN group (95% CI -4.35 - 2.73 days); very low certainty evidence.

v. Duration of mechanical ventilation: mean duration of ventilation was 3 days longer in the IFN group than the control group (95% CI 0.09 - 5.99); very low certainty evidence (Figure 6).

vi. Adverse reactions: there were fourteen adverse effects reported in the IFN group compared to one in the control group (Risk ratio 14; 95% CI 1.92 - 102.13); very low certainty evidence (Figure 7).

vii. Serious adverse events day 14 – 28: not specifically reported. There was 1 hypersensitivity reaction attributed to interferon β-1a.

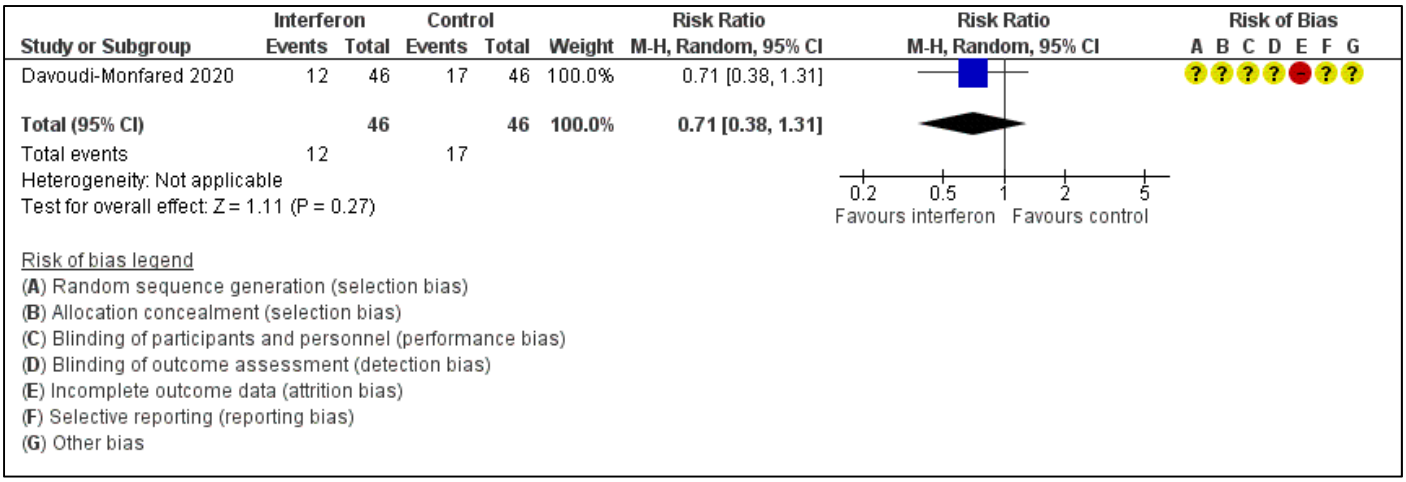

Figure 4. Forest plot of death at day 28 using an intention to treat analysis (Davoudi-Monfared 2020)

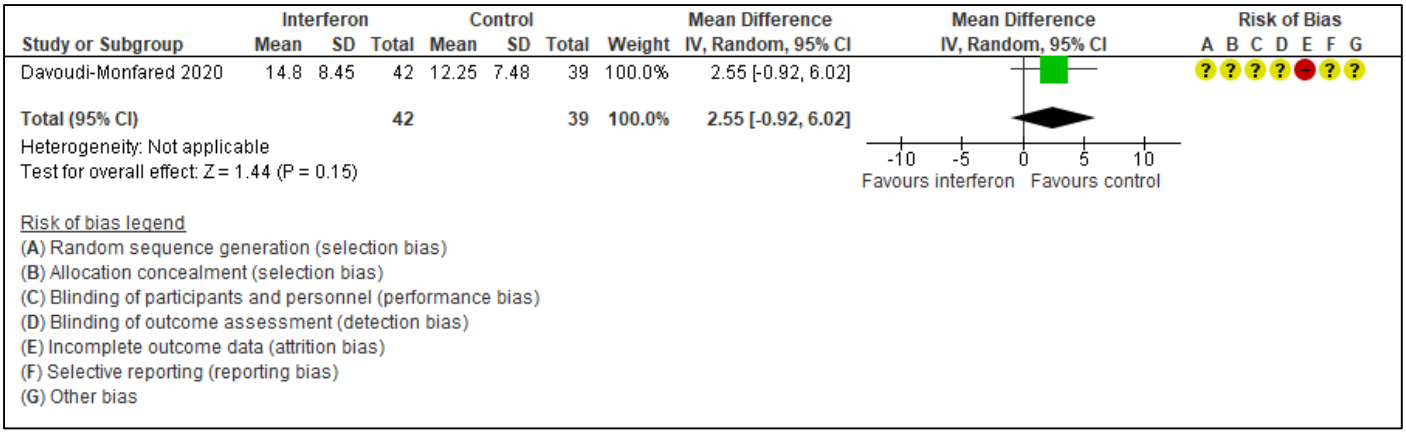

Figure 5. Forest plot of duration of hospitalisation (Davoudi-Monfared 2020)

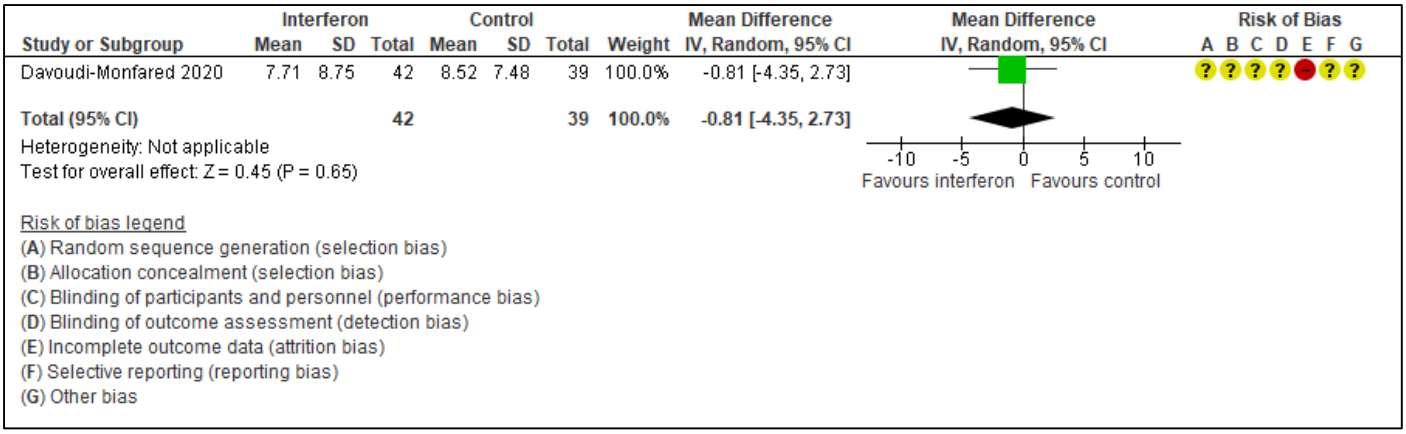

Figure 6. Forest plot of duration of ICU stay (Davoudi-Monfared 2020)

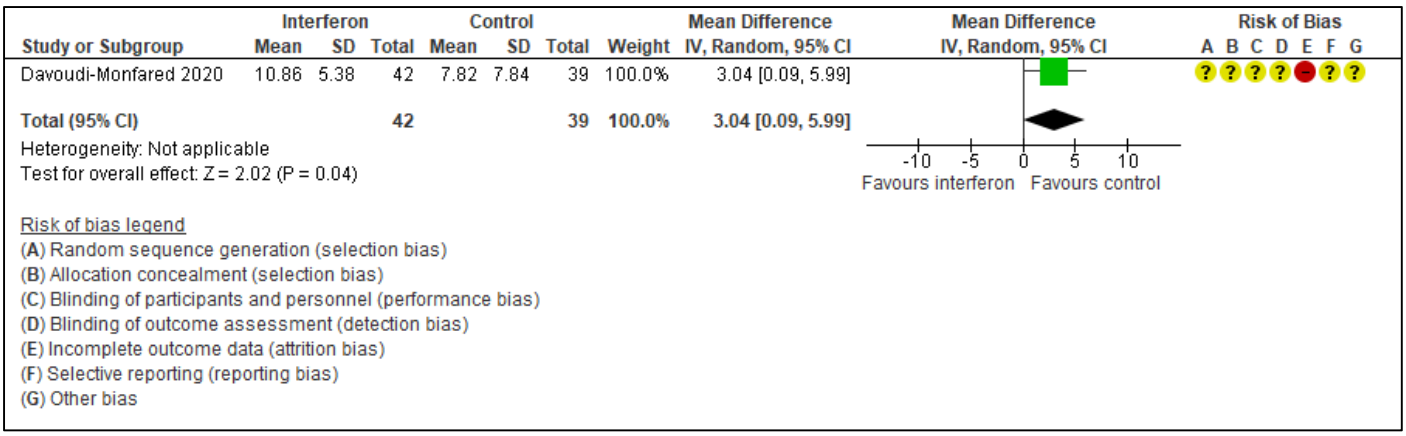

Figure 7. Forest plot of duration of mechanical ventilation (Davoudi-Monfared 2020)

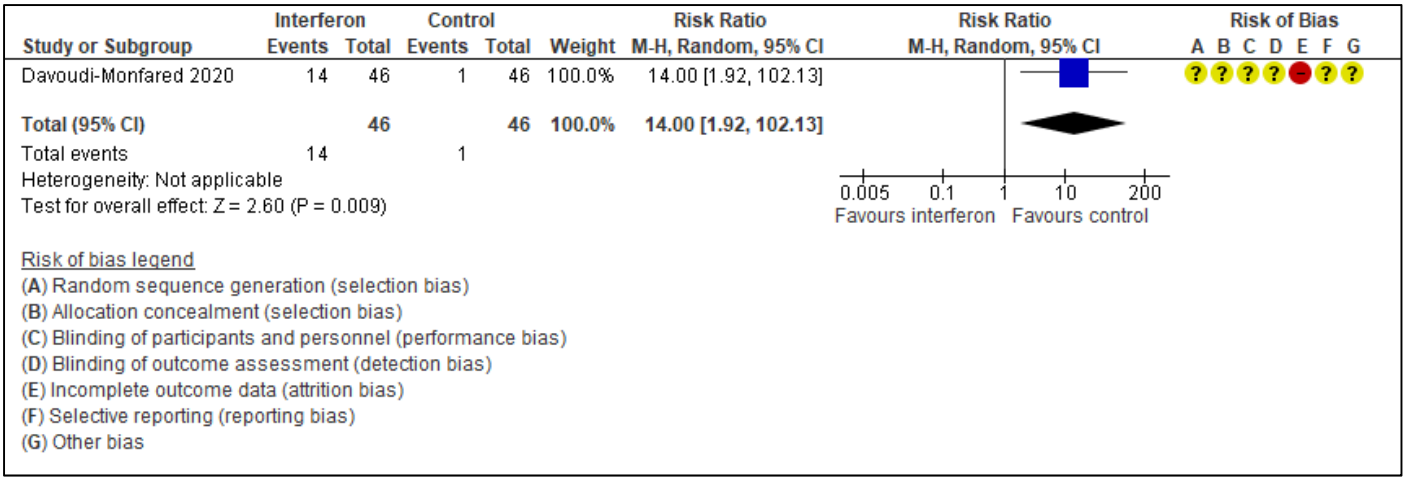

Figure 8. Forest plot of adverse effects by ITT analysis (Davoudi-Monfared 2020)

Sensitivity analyses

Refer to appendix 2 for the sensitivity analyses of the conducted ITT analysis (Davoudi-Monfared 2020). For mortality, the results differ between the three imputation methods (assuming no deaths in the control, or all deaths or applying the observed death rate). This indicates instability in results and uncertainty in the effect. For adverse effects, all three imputation methods favour the control - showing stability among the results when considering different assumptions.

CONCLUSION

In this update of the rapid review, we identified two randomised controlled trials.

The first of these evaluated interferon β -1b in combination with ribavirin and lopinavir/ritonavir, compared to lopinavir/ ritonavir, in hospitalized patients with mild disease (n = 127) (Hung 2020). There were no deaths reported. There was low certainty evidence that there may be a benefit of this combination in terms of the duration of hospitalization (9 vs 14.5 days). No benefit was seen for other clinical outcomes. There may be a 4-fold more rapid time to RT-PCR negativity, but it is unclear whether this has any clinical benefit. This trial studied a combination intervention, and it is unclear how much of the benefit observed can be attributed to interferon β-1b.

The second trial evaluated interferon β-1a plus standard of care compared to standard of care (which included hydroxychloroquine and lopinavir/ritonavir or atazanavir/ritonavir) in hospitalised patients with severe disease (n = 92) (Davoudi-Monfared 2020). We assessed this study as providing very low certainty evidence due to the serious risk of bias, small sample size and low event rates. On an intention-to-treat analysis prepared for this rapid review, there were 12 deaths in the IFN and 17 in the control group (RR 0.71; 95% CI 0.38 - 1.31). Participants in the IFN arm required longer mechanical ventilation, and experienced more adverse effects.

We found no studies of interferons compared with placebo. We found no studies in children.

Based on the available data, we do not recommend the inclusion of interferons, with or without other medicines, in treatment guidelines for COVID-19 in South Africa. Eligible patients in South Africa should be considered for enrolment in randomised clinical trials so that robust data on efficacy and safety of interventions can be generated to inform treatment policies going forward.

Reviewers: Tamara Kredo, Karen Cohen, Yusentha Balakrishna.

Declaration of interests: TK (Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Stellenbosch University; South African GRADE Network), KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town), YB (Biostatistics Research Unit, South African Medical Research Council) have no interests to declare in respect of interferon therapy for COVID-19.

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Table 1. Characteristics of included trials

Citation	Study design	Population	Treatment	Main findings	Risk of Bias assessment
1. Hung LF et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020. DOI 10.1016/S0140-6736(20)31042-4 pubmed.ncbi.nlm.nih.gov/32401715	Randomised controlled trial Multi-centre Primary endpoint: time to achieve a negative RT-PCR result for SARS-CoV-2 in a nasopharyngeal swab sample Secondary clinical endpoints: time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h daily NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay 30-day mortality. frequencies and duration of adverse events. Secondary virological endpoints: the time to achieve negative SARS-CoV-2 RT-PCR in all clinical samples daily viral load changes in the first 7 days emergence of amino acid mutations in the *nsp5* gene encoding a 3C-like protease.	Setting: Hong Kong Follow-up: 30 days 127 participants with confirmed infection and mild disease. 86 assigned to the combination therapy arm, of which 52 were admitted to hospital less than 7 days from symptom onset. 52 years, 54% men median time from symptom onset to admission 5 days (IQR 3-7). Disease severity in all mild by NEWS2 and SOFA criteria Inclusion criteria: adult patients >18 years hospitalised for virologically confirmed SARS-CoV-2 infection; NEWS of >1 upon recruitment 3; auditory temperature >38°C or other symptoms including cough, sputum production, sore-throat, nasal discharge, myalgia, headache, fatigue or diarrhoea upon admission; symptom duration<14 days; all subjects give written informed consent. For patients who were critically ill, requiring ICU, ventilation or confused, informed consent was obtained from spouse, next-of-kin or legal guardians.; subjects had to be available to complete	Intervention (n = 86) Lopinavir + Ritonavir for 14 days + Ribavirin for 14 days + 1-3 doses of Interferon-b-1b (400mg/100mg/400mg) administered subcutaneously Interferon was only given to those recruited up to 7 days post onset of symptoms. Comparator (n = 41) Lopinavir + Ritonavir (400mg) Duration: 14 days Treatment with interferon beta-1b depended on the time from symptom onset: participants recruited and treated between days 7 and 14 from symptom onset did not receive interferon beta-1b, whereas participants recruited and treated up to day 7 received interferion beta-1b. Randomization was not stratified.	Primary endpoint: Intervention group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4・37 [95% CI 1・86–10・24], p=0・0010. Clinical improvement better in the combination group: shorter time to complete alleviation of symptoms, defined as a NEWS2 of 0 (4 days [IQR 3–8] in the combination group *vs* 8 days [IQR 7–9] in the control group; HR 3.92 [95% CI 1.66–9.23], p<0・0001) and SOFA score of 0 (3.0 days [1–8] *vs* 8.0 days [6.5–9]; HR 1.89 [1.03–3.49], p=0.041; Shorter median hospital stay in the combination group than in the control group (9.0 days [7.0–13.0] *vs* 14.5 days [9.3–16.0]; HR 2.72 [1.2–6.13], p=0.016). Virological outcome: combination treatment associated with significantly shorter time to negative viral load in all specimens When assessed individually and combined: Adverse events reported by 41 (48%) of 86 patients in the combination group and 20 (49%) of 41 patients in the control group. Most common adverse events were diarrhoea	Risk of bias 2.0 (www.covid-nma.com) found some potential concerns due to lack of blinding which may affect the subjective outcomes such as time to clinical improvement, but overall other aspects of the trial reporting were adequate.

	serum cytokine response	the study and comply with study procedures; willingness to allow for serum samples to be stored beyond the study period, for potential additional future testing to better characterize immune response. Exclusion criteria: Inability to comprehend and to follow all required study procedures; Allergy or severe reactions to the study drugs; Patients with known prolonged QTc syndrome, ventricular cardiac arrhythmias, including torsade de pointes, second or third degree heart block, QTc interval >480ms; Patients taking medication that will potentially interact with lopinavir/ ritonavir, ribavirin or interferon b-1b; Patients with known history of severe depression; Pregnant or lactating women; Received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 1 month prior to recruitment in this study or expect to receive an experimental agent during this study; have a history of alcohol or drug abuse in the last 5 years; any condition that the investigator believes may interfere with successful completion of the study.		(52 [41%] of 127 patients), fever (48 [38%] patients), nausea (43 [34%]) and raised alanine Transaminase level (18 [14%]. Adverse events mostly resolved within 3 days after drug initiation. Sinus bradycardia in four (3%) patients. No difference in incidence or durations of adverse events between groups. Peak median alanine transaminase concentration was 38・0 units per L (24.5–62.5) and peak median bilirubin was 22.0 µmol/L (17.0–32.5), in all patients. No serious adverse events reported in the combination group. One patient in control group had serious adverse event of impaired hepatic enzymes requiring discontinuation of treatment. No deaths.	

2. Title: Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomized clinical trial **Authors** **Effat Davoudi-Monfared, edavudimonfared@gmail.com, Department of Pharmacotherapy, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.**	Open label randomized clinical trial Setting: Hospital in Tehran, Iran Follow up: 4 weeks Primary outcome: time to reach clinical response (days). Clinical response was defined according to the six-category ordinal scale [19]. This scale classifies patients in six categories according to the severity of the viral pneumonia. The six categories are: (1) discharge (2) hospital admission, not requiring oxygen (3) hospital admission, requiring oxygen (4) hospital admission, requiring non-invasive positive pressure ventilation (5) hospital admission requiring invasive mechanical ventilation (6) death. Time to clinical response was considered days required to at least two scores improvement in the scale or patient's discharge, which one that occurred sooner. Secondary outcomes:	N=92 randomised, 81 analysed-42 IFN, 39 control. This is reported as due to "drop outs" however 4 died in IFN group during IFN dosing, and 7 dropped out of control arm to join another trial Mean age: 58 yrs 44/81 were male Hypertension (38.3%), cardiovascular diseases (28.4%), diabetes mellitus (27.2%), endocrine disorders (14.8%), and malignancy (11.1%) were common baseline diseases. Inclusion criteria: Adult patients admitted to hospital with severe COVID-19 infection: (1) hypoxemia (need for noninvasive or invasive respiratory support to provide capillary oxygen saturation above 90%) (2) Hypotension (systolic blood pressure less than 90 mmHg or vasopressor requirement) (3) renal failure secondary to COVID-19 (according to KDIGO definition) (4) neurologic disorder secondary to COVID-19 (decrease of 2 or more scores in Glasgow Coma Scale) (5) thrombocytopenia secondary to COVID-19 (platelet count less than 150000 /mm3) (6)	Intervention: IFN β-1a in addition to the standard of care:44 micrograms/ml (12 million IU/ml) of interferon β-1a (ReciGen®, CinnaGen Co., Iran) was injected subcutaneously three times weekly for two consecutive weeks. Standard of care: (the hospital protocol) consisted of hydroxychloroquine (400 mg BD in first day and then 200 mg BD) plus lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) for 7-10 days. Also primary care, respiratory support, fluid, electrolytes, analgesic, antipyretic, corticosteroid and antibiotic were recommended in the hospital protocol if indicated. 26 (62%) of interferon and 15 (44%) of control participants received corticosteroids.	Only the per protocol analysis is presented in the paper. We have also performed an intention to treat (ITT) analysis for categorical outcomes. Time to the clinical response was similar in IFN and the control groups (9.7 ± 5.8 vs. 8.3 ± 4.9 days respectively, p=0.95). Investigators reported lower 28-day overall mortality in the IFN group (8 versus 17 deaths). However this excludes 4 deaths, all in the IFN arm, which were omitted from the analysis. These deaths occurred during interferon dosing; 2 had received 1 dose, and 2, 2 doses of interferon. When these deaths are included in an ITT, there are 12 deaths in the interferon group and 17 in the control group, RR 0.71 (95% CI 0.38 to 1.31) Investigators report that "Early administration (<10 days after symptom onset) significantly reduced mortality (OR=13.5; 95% CI: 1.5-118). However, late administration of INF did not show significant effect (OR=2.1; 95% CI: 0.48-9.6)." It is unclear how this analysis was performed, and how participants receiving IFN 10 days after symptom onset were categorised. On day 14, 67% vs. 44% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05- 6.37). NOTE: this is not specified as an endpoint in the methods	Risk of Bias 2.0 (www.covid-nma.com) reported **high risk of bias** Based on missing outcome data Comment: 92 randomized/81 analysed. Four patients in the intervention arm were excluded because they died before finishing the first week treatment (i.e., received <3 doses of IFN). The reason for missing data is associated with the outcome for mortality, time to clinical improvement and WHO clinical progression scale outcomes (estimated using an ordinal scale that takes death into account). Seven patients in the control arm were excluded because the left the study to enter another trial. Risk assessed to be high for the outcomes: Mortality. Time to clinical improvement. WHO clinical progression scale score 6 and above. WHO clinical progression scale score 7 and above. There were also concerns with the reporting on randomisation and allocation concealment, lack of blinding and unclear

	Duration of mechanical ventilation, duration of hospital stay, length of ICU stay, 28-day mortality, effect of early or late (before or after 10 days of onset of the symptoms) administration of IFN on mortality, adverse effects and complications during the hospitalization. The Naranjo scale was used for evaluation of adverse effects of IFN.	severe gastrointestinal symptoms secondary to COVID-19 (vomiting/diarrhea that caused at least mild dehydration). Exclusion criteria: allergy to IFNs, receiving IFNs for any other reasons, previous suicide attempts, alanine amino transferase (ALT) > 5× the upper limit of the normal range and pregnant women.		Duration of mechanical ventilation was similar(days ± SD) IFN 10.86 ± 5.38 vs 7.82 ± 7.84 , p=0.47 Length of hospital stay (days ± SD) was similar IFN 14.80 ± 8.45 vs 12.25 ± 7.48, p= 0.69 Length of ICU stay (days ± SD) was similar IFN 7.71 ± 8.75 vs 8.52 ± 7.48, p=0.42 **Complications IFN vs SOC:** Acute kidney injury 12 (29%) vs 11 (28%), p=0.58 Nosocomial infections 11 (26%) vs 5 (13%) p=0.09 Septic shock 10 (24%) vs 7 (18%), p=0.35 Hepatic failure 5 (12%) vs 9 (23%), p=0.15 DVT 1 (2%) vs 0, p=0.51 **Adverse effects** IFN vs SOC: By ITT, RR for adverse effect 14 (95% CI 1.92 to 102.13) Hypersensitivity reactions 1 (2%) vs 0 p=0.51 IFN-related injection reactions 8(19%) vs 0 Neuropsychiatric problems 4 (10%) vs 0 p=0.06 Indirect hyperbilirubinemia 1 (2%) vs 1 (3%) p= 0.73	risk of selective outcome reporting (no protocol was available).

Table 2. Summary of findings: Hung 2020

Lopinavir/ritonavir, ribavirin and interferon β-1b compared to lopinavir/ ritonavir alone for managing COVID-19

Patient or population: adult patients >18 years hospitalised for virologically confirmed SARS-CoV-2 infection
Setting: Hong Kong
Intervention: lopinavir/ritonavir, ribavirin and interferon β-1b
Comparison: lopinavir/ ritonavir alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lopinavir/ ritonavir alone	Risk with lopinavir/ritonavir, ribavirin and interferon β-1b				
Mortality follow up: 30 days	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	127 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	
Time to discharge follow up: 30 days	The median duration of hospitalization was **14.5** days	HR **2.72 days higher** (1.2 higher to 6.13 higher)	-	127 (1 RCT)	⊕⊕◯◯ LOW [a,c]	Lopinavir/ritonavir, ribavirin and interferon β-1b may decrease the duration of hospitalization.
Time to RT PCR negativity follow up: 30 days	The median duration of viraemia was **12** days	HR **4.37 higher** (1.86 higher to 10.24 higher)	-	127 (1 RCT)	⊕⊕◯◯ LOW [a,c]	Lopinavir/ritonavir, ribavirin and interferon β-1b may decrease the duration of viraemia.
Duration of ICU stay - not reported	-	-	-	-	-	
Duration of respiratory support - not reported	-	-	-	-	-	
Adverse reactions follow up: range 14 days to 28 days	488 per 1,000	**478 per 1,000** (327 to 698)	**RR 0.98** (0.67 to 1.43)	127 (1 RCT)	⊕⊕◯◯ LOW [a,c]	Lopinavir/ritonavir, ribavirin and interferon β-1b may make little to no difference in adverse reactions.
Serious adverse events follow up: range 14 days to 28 days	24 per 1,000	**4 per 1,000** (0 to 94)	**RR 0.16** (0.01 to 3.87)	127 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	Lopinavir/ritonavir, ribavirin and interferon β-1b may reduce serious adverse events but the evidence is very uncertain.

***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; **HR:** Hazard ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded by one level for indirectness - Single trial in one setting that may not be generalisable to other settings.
b. Downgraded by two levels for imprecision - Small sample size and low event rate.
c. Downgraded by one level for imprecision - Small sample size.
d. Downgraded by two levels for imprecision - Small sample size and very wide confidence interval.

Table 3. Summary of findings: Davoudi-Monfared 2020

Interferon β-1a plus standard of care compared to standard of care for managing COVID-19

Patient or population: Adult patients admitted to hospital with severe COVID-19 infection
Setting: Hospital in Tehran, Iran
Intervention: Interferon β-1a plus standard of care
Comparison: Standard of care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	Risk with interferon β-1a plus standard of care				
Mortality follow up: 28 days	370 per 1,000	**262 per 1,000** (140 to 484)	**RR 0.71** (0.38 to 1.31)	92 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Interferon β-1a plus standard of care may have little to no effect on mortality but the evidence is very uncertain.
Duration of hospitalisation follow up: 28 days	The mean duration of hospitalisation was **12.25** days	MD **2.55 days more** (0.92 fewer to 6.02 more)	-	81 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Interferon β-1a plus standard of care may increase the duration of hospitalisation but the evidence is very uncertain.
Duration of viraemia - not reported	-	-	-	-	-	
Duration of ICU stay follow up: 28 days	The mean duration of ICU stay was **8.52** days	MD **0.81 days fewer** (4.35 fewer to 2.73 more)	-	81 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Interferon β-1a plus standard of care may slightly reduce the duration of ICU stay but the evidence is very uncertain.
Duration of mechanical ventilation follow up: mean 28 days	The mean duration of mechanical ventilation was **7.82** days	MD **3.04 days more** (0.09 more to 5.99 more)	-	81 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Interferon β-1a plus standard of care may increase the duration of mechanical ventilation but the evidence is very uncertain.
Adverse reactions follow up: 28 days	22 per 1,000	**304 per 1,000** (42 to 1,000)	**RR 14.00** (1.92 to 102.13)	92 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Interferon β-1a plus standard of care may increase adverse reactions but the evidence is very uncertain.
Serious adverse events - not reported	-	-	-	-	-	

*__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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded by one level for risk of bias - The trial was appraised as having high risk of bias due to poor reporting of the outcome data, in particular, excluding participants who had been randomised and had died from the analysis. There was also no blinding and poor reporting on randomisation and allocation concealment.
b. Downgraded by one level for indirectness - Evidence from one trial in one setting that may not be generalisable to other settings.
c. Downgraded by one level for imprecision - Small sample size and low event rates.

Table 4. Characteristics of observational studies from previous review (March 2020)

Citation	Study design	Population (n)	Treatment	Main findings
Abstract only Wei R, Zheng N, Jiang X, Ma C, Xu X, Liu S, et al. Early antiviral therapy of abidor combined with lopinavir/ritonavir and re-combinant interferonα-2b in patients with novel coronavirus pneumonia in Zhejiang: A multicenter and prospective study. Chinese Journal of Clinical Infectious Diseases. 2020. https://www.epistemonikos.org/documents/463497c3672fac35e144adc2d3ef1792c1862eb5	Prospective cohort to compare triple vs dual treatment and timing of triple therapy [dates not clear]	Setting: China, 15 medical institutions of Zhejiang Province Patients: hospitalized with COVID-19 pneumonia Sample size: possibly 236	All patients were treated with recombinant interferon α-2b (5 million U, 2 times/d) aerosol inhalation. 196 patients were treated with abidol (200 mg, 3 times/d) + lopinavir + ritonavir (dose unclear) as the triple combination antiviral treatment group. 41 patients were treated with lopinavir + ritonavir (dose unclear) as the dual combination antiviral treatment group. Sub-group analysis: patients who received triple combination antiviral therapy divided into three groups: within 48 hours, 3-5 days and > 5 days after the symptom onset.	Cannot determine efficacy or safety of interferon as all patients received this therapy. The time to virus nucleic acid negative was 12.2 ± 4.7 days in the triple combination antiviral drug group, which was shorter than that in the dual combination antiviral drug group (15.0 ± 5.0) days (t = 6.159, P < 0.01). The length of hospital stay [12 days (9, 17)] in the triple combination antiviral drug group was also shorter than that in the dual combination antiviral drug group [15 days (10, 18)] (H = 2.073, P < 0.05). Comparing the antiviral treatment which was started within 48 hours, 3-5 days and > 5 days after the symptom onset of triple combination antiviral drug group, the time from the symptom onset to the negative test of viral shedding was 13 (10,16.8), 17 (13,22) and 21 (18-24) days respectively (Z = 32.983, P < 0.01), and the time from antiviral therapy to the negative test of viral shedding was (11.8±3.9) , (13.5±5.1) and (11.2±4.3) d. The differences among the three groups were statistically significant (Z=32.983 and 6.722, P <0.01 or<0.05)

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer reviewed Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing. Journal of medical virology. 2020. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25783	Prospective case series Period: Jan 23 – Feb 8, 2020	Setting: China, Chongqing Patients: 135 hospitalized of which 40 had severe disease and 95 mild disease (criteria for mild versus severe not specified). Age: 47 years (IQR 36-55), and there was no significant gender difference (53.3% men) Forty-three (31.9%) patients had underlying disease, primarily hypertension (13 [9.6%]), diabetes (12 [8.9%]), cardiovascular disease (7 [5.2%]), and malignancy (4 [3.0%]) Patients with severe disease were older and more likely to have comorbidities. All patients had radiographic evidence of lung involvement.	135 patients received: lopinavir + ritonavir and interferon. 59 received antibacterial therapy 36 received corticosteroids. 124 patients received traditional Chinese medicine too.	Cannot determine efficacy or safety of interferon as all patients received this therapy. By Feb 8, 5 patients had been discharged, one patient had died
Online only, not peer reviewed Liu l, Gao J-y. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. 2020. https://www.medrxiv.org/content/medrxiv/early/2020/02/23/2020.02.20.20025536.full.pdf	Retrospective, single-center case series Period: Jan – Feb 2020	Setting: China, Chongqing University, Three Gorges Hospital 51 Patients admitted between January 20 to February 3, 2020 Discharged January 29 to February 11, 2020 44 non-severe; 7 severe Median age was 45 years (interquartile range, 34-51; range, 16-68 years) and 32 (62.7%) were men.	All received aerosolised inhalation of recombinant human interferon a-1b for injection and oral antiviral therapy with lopinavir + ritonavir, duration not specified. Most patients were given Bacillus licheniformis capsules regulated intestinal flora treatment (44 [86.3%]). 10 patients (19.6%) received short-term (3-5 days) glucocorticoid treatment.	Cannot determine efficacy or safety of interferon as all patients received this therapy. 1 patient died All others discharged

Citation	Study design	Population (n)	Treatment	Main findings
Google translated article, English abstract available Jun C, Yun L, Xiuhong X, Ping L, Feng L, Tao L, et al. Efficacies of lopinavir/ritonavir and abidol in the treatment of novel coronavirus pneumonia. Chinese Journal of Infectious Diseases. 2020;38(00):E008-E. http://rs.yiigle.com/yufabiao/1182592.htm	Retrospective case series Period: January 20 to February 6, 2020	Setting: China, Shanghai Public Health Clinical Center Patients: 134 hospitalised COVID-19 patients with pneumonia Sex: 69 males and 65 females Age: 35 to 62 years, with an average age of 48 years	134 patients received recombinant human interferon α2b spray treatment and symptomatic supportive treatment. 52 patients took the antiviral drug lopinavir + ritonavir, 34 patients took the antiviral drug abidol, and 48 patients did not take any antiviral medication.	Cannot determine efficacy or safety of interferon as all patients received this therapy.

Table 5. List of planned and ongoing studies (source: www.covid-nma.com 11 June 2020)

Treatment (per arm)	Sample size	Severity at enrollment	Funding	Reg. number
(1) Umifenovir *vs* (2) Umifenovir + interferon alpha	100	Moderate/severe	Tongji Hospital	NCT04254874
(1) Remdesivir *vs* (2) Chloroquine *vs* (3) Hydroxychloroquine *vs* (4) Lopinavir + ritonavir + interferon beta1 *vs* (5) Standard of care	1000	Moderate/severe/critical	Vilnius University Hospital Santaros Klinikos	EUCTR2020-001366-11-LT
(1) Recombinant super-compound interferon (rSIFN-co) *vs* (2) Interferon alpha	100	Moderate/severe	West China Hospital, Sichuan University	ChiCTR2000029638
(1) Antiviral therapy + TCM *vs* (2) Antiviral therapy + TCM + interferon alpha2b *vs* (3) Antiviral therapy + TCM *vs* (4) Antiviral therapy + TCM + interferon alpha2b	480	Moderate/severe	The First Affiliated Hospital of Medical College of Zhejiang University	ChiCTR2000029573
(1) Interferon alpha2b *vs* (2) Lopinavir + ritonavir *vs* (3) Lopinavir + ritonavir + interferon alpha2b	90	No restriction on type of patients	The First Hospital of Changsha; The Second Xiangya Hospital of Central South University	ChiCTR2000029496
(1) Interferon alpha1b + ribavirin *vs* (2) Lopinavir + ritonavir + interferon alpha1b *vs* (3) Lopinavir + ritonavir + ribavirin + interferon beta1	108	Mild/moderate	Chongqing Public Health Medical Center	ChiCTR2000029387
(1) Lopinavir + ritonavir *vs* (2) Dexamethasone *vs* (3) Interferon beta 1a *vs* (4) Hydroxychloroquine *vs* (5) Placebo	2500	Moderate/severe/critical	University of Oxford	2020-001113-21
(1) Remdesivir *vs* (2) Lopinavir + ritonavir *vs* (3) Lopinavir + ritonavir + interferon beta1 *vs* (4) Hydroxychloroquine *vs* (5) Standard of care	3100	Moderate/severe/critical	Institut National de la SantÃ© Et de la Recherche MÃ©dicale, France	NCT04315948
(1) Umifenovir + interferon alpha + bromhexine *vs* (2) Umifenovir + interferon alpha	60	Mild	Second Affiliated Hospital of Wenzhou Medical University	NCT04273763
(1) Lopinavir + ritonavir + ribavirin + interferon beta1 *vs* (2) Lopinavir + ritonavir	70	Mild/moderate	The University of Hong Kong	NCT04276688
(1) Xiyanping injection + Lopinavir/ritonavir + alpha-interferon nebulization *vs* (2) Lopinavir + ritonavir + interferon alpha	348	Mild/moderate	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04275388
(1) Interferon beta 1a *vs* (2) Standard of care	30	No restriction on type of patients	Tehran University of Medical Sciences	IRCT20100228003449N28
(1) Interferon beta 1a *vs* (2) Standard of care	30	No restriction on type of patients	Tehran University of Medical Sciences	IRCT20100228003449N27
(1) Interferon beta 1a *vs* (2) Placebo	400	No restriction on type of patients	Synairgen Research Limited	EUCTR2020-001023-14-GB
(1) Interferon alpha2a + ribavirin *vs* (2) Umifenovir + ribavirin	30	Mild/moderate	Foshan First People's Hospital	ChiCTR2000030922
(1) Remdesivir *vs* (2) Chloroquine *vs* (3) Lopinavir + ritonavir *vs* (4) Lopinavir + ritonavir + interferon beta *vs* (5) Standard of care	N/A	Moderate/severe/critical	Multiple funders including the World Health Organization (Switzerland)	ISRCTN83971151

Appendix 1: Search strategy

Epistemonikos Living Overview of the Evidence (love) **11 May 2020 (**https://app.iloveevidence.com/topics) **Search:** interferon **Number of studies:** 89 records
Cochrane COVID-19 Study Register **11 May 2020 (**https://covid-19.cochrane.org/) **Search Strategy:** Interferon **Number of studies:** 110 records found, 28 duplicates removed = 88 records

Appendix 2: Sensitivity analysis

Table 5. Sensitivity analyses

Outcome	Imputation: Best case scenario (all missing did not experience the outcome)	Imputation: Worst case scenario (all missing experienced the outcome)	Imputation: Assuming similar rate as observed
Mortality on day 28	12 (IG) vs 17 (CG) deaths RR 0.71 (95% CI 0.38, 1.31)	12 (IG) vs 24 (CG) deaths RR 0.50 (95% CI 0.29, 0.87)	12 (IG) vs 20 (CG) deaths[a] RR 0.60 (95% CI 0.33, 1.08)
Adverse effects	14 (IG) vs 1 (CG) adverse effects RR 14 (95% CI 1.92, 102.13)	18 (IG) vs 8 (CG) adverse effects RR 2.25 (95% CI 1.09, 4.65)	15 (IG) vs 1 (CG) adverse effects[b] RR 15 (95% CI 2.07, 108.92)

(Abbreviations: IG = interferon group; CG = control group; RR = risk ration; CI = confidence interval)

[a] 43.6% CG death rate applied to 7 participants results in imputing 3 deaths

[b] 33.3% IG adverse effects rate applied to 4 participants results in imputing 1 adverse effect

[b] 2.6% CG adverse effects rate applied to 7 participants results in imputing 0 adverse effects

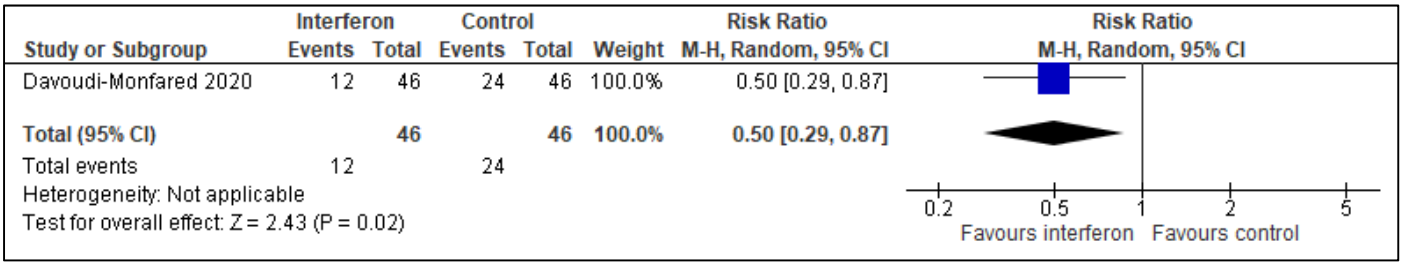

Figure 9. Forest plot of mortality at day 28 – sensitivity analysis (worst case scenario)

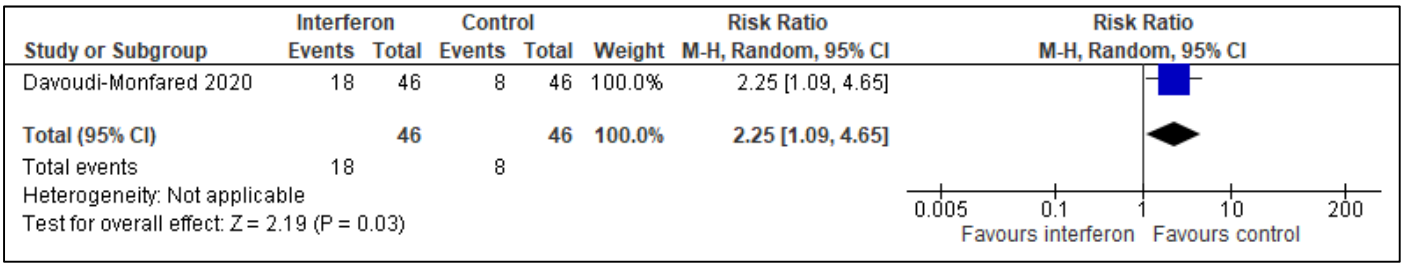

Figure 10. Forest plot of adverse effects – sensitivity analysis (worst case scenario)

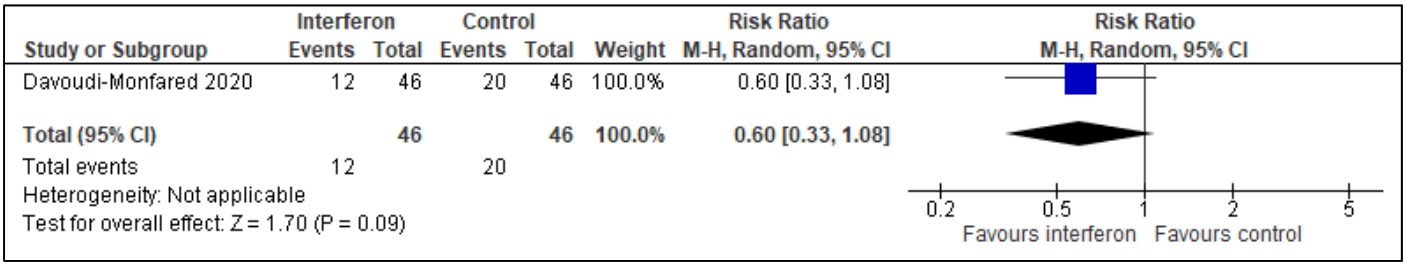

Figure 11. Forest plot of mortality at day 28 – sensitivity analysis (similar rate scenario)

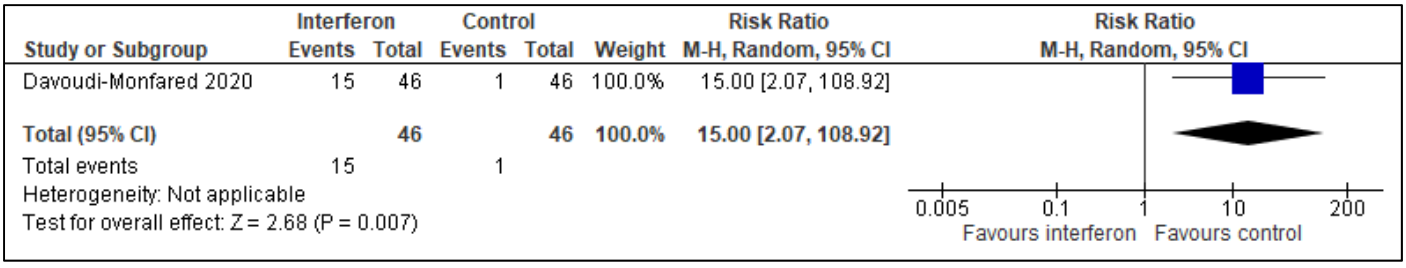

Figure 12. Forest plot of adverse effects – sensitivity analysis (similar rate scenario)

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: ☐ None: ☐ Uncertain: x	Hung *et al*. RCT (n = 127) comparing lopinavir/ritonavir (LPV/r), ribavirin and interferon beta-1b with LPV/r in hospitalised adult patients with mild disease that found low certainty evidence that there may be shorter hospital stay (5.5 days) and 4-fold faster time to viral clearance. No deaths. Need for ventilatory support not reported. Davoudi-Monfared et al RCT (n=92, investigators only report per protocol analysis in 81) compared interferon beta-1a in hospitalised patients, majority with comorbidities, severe disease.High risk of bias. On intention to treat analysis, 12 deaths in the IFN and 17 in the control group, RR for death 0.71 (95% CI 0.38, 1.31). Participants in the IFN arm required longer mechanical ventilation, and there were more adverse effects in the IFN arm.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: x Small: ☐ None: ☐	Hung *et al*: AEs similar in 2 arms, and mostly attributed to LPV/r More adverse effects in interferon arm than control in Davoudi-Monfared *et al*. One hypersensitivity reaction in interferon arm.
BENEFITS & HARMS	**Do desirable effects outweigh undesirable harms?** Favours intervention: ☐ Favours control: ☐ Intervention = Control *or* Uncertain: x	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☐ Very low: x	*High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: ☐ No: ☐ Uncertain: x	SAHPRA-registered products: Rebif 22 (INF-β1a), Rebif 44 (INF-β1a), Pegasys (pegINF-α2a), Intron A 10 miu (INF-α-2b), Avonex (INF-β1a), Plegridy (pegINF-α2a), Betaferon (INF-β1b). *Note:* Intron A is not marketed locally, may be accessed via S21 from relevant countries; Available stock currently covers MS indication.
RESOURCE USE	**How large are the resource requirements?** More intensive: x Less intensive: ☐ Uncertain: ☐	**Price of medicines:** **Medicine (pack size), Trade name®** | **Tender price*** | **SEP**** INF-β1a, 30mcg/ml (4), Avonex® | R4547.54 | R7640.00 INF-β1b, 0.25mg/ml (1), Betaferon® | R418.64 | R506.67 INF-β1a, 44mcg/ml (12), Rebif 22® | n/a | R6859.67 INF-β1a, 88mcg/ml (12), Rebif 44® | n/a | R7641.67 *Contract circular RT290-2018 [Accessed 10 June 2020] ** SEP price [Accessed 10 June 2020] https://mpr.code4sa.org/
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: x Major: ☐ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: ☐ No: ☐ Uncertain: x	People with COVID-19 would probably value reduced hospital time, but we have not data on this. No data about acceptability.
EQUITY	**Would there be an impact on health inequity?** Yes: ☐ No: ☐ Uncertain: x	This would depend on access and capacity to deliver the intervention to all who need it. We have not data on this.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	29 March 2020	TK, KC	Insufficient evidence to support use of interferon. May be used in a clinical trial setting.
Second	31 July 2020	TK, KC, YB	Recommendation retained as above, noting that interferon is cost-prohibitive. Evidence and EtD updated, including an ITT with sensitivity analyses.