Remdesivir for COVID#19: evidence review of the clinical benefit and harm

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

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

Date: 24 June 2020, Update of first version (16 April 2020)

Key findings

- We conducted a rapid review of available clinical evidence about use of remdesivir, with or without other medicines, for hospitalised patients with COVID-19 requiring oxygen or ventilation.
- We found two randomized controlled clinical trials examining remdesivir versus placebo and a meta-analysis of these trials. The details of a compassionate use cohort as well as an open label cohort study have also been published.
- One RCT showed that remdesivir shortened median time to recovery from 15 to 11 days; while the other RCT (which was underpowered as it could not complete recruitment) demonstrated no statistically significant benefits in terms of any outcomes. A meta-analysis of the two RCTS showed that remdesivir decreased the risk of disease progression to requiring ventilation. There were no statistically significant differences in the rates of adverse events between remdesivir and placebo in either trial.
- One RCT showed no difference in outcomes between a five-day course and a ten-day course of remdesivir.
- We identified no reports on the use of remdesivir in children with COVID-19, although a clinical trial is planned in this group.
- There are several ongoing clinical trials which will provide additional data on benefits and harms of remdesivir in the management of patients with COVID-19.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

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

Recommendation: Based on this evidence review, the NEMLC Subcommittee suggests that remdesivir not be recommended for treatment of hospitalised patients with COVID-19 requiring oxygen or ventilation.
Rationale: The included studies suggest some benefit for remdesivir compared with placebo for time to recovery in severe COVID-19 disease and no significant difference in the rate of adverse events. However, there were no statistically significant differences in mortality. The medicine is expensive and scale of volume procurement will affect the price. The medicine is not currently SAHPRA registered and may be accessed through S21 application process. Availability of limited S21 supplies would impact equity.
Level of Evidence: RCTs of low to moderate 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

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolised to an analogue of adenosine triphosphate that inhibits viral RNA polymerases.

Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses[1, 2, 3].

RESEARCH QUESTION: Is there evidence to support the use of remdesivir in the management of COVID-19 in hospitalised patients requiring oxygen or ventilation?

METHODS

We conducted a rapid review of the evidence including systematic searching of two electronic databases (PubMed and the Epistemonikos). The Clinicaltrials.gov database was also checked for registered studies, and the Cochrane living systematic reviews website within the Cochrane library was also checked. Screening of records and data extraction was conducted by one reviewer, with results reviewed and checked by another reviewer. Relevant records were extracted in a narrative table of results. The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age, but severe disease requiring oxygen or ventilatory assistance.

Intervention: Remdesivir either alone or in combination with other medicines. 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, duration of ICU stay, duration of respiratory support, adverse reactions.

Study designs: Case reports, case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans.

RESULTS

We searched PubMed and the Epistemonikos electronic databases on 10 June 2020. We also searched the ClinicalTrials.Gov database. Details of each search are provided in Appendix 1. One reviewer screened 223 records and identified two eligible articles as published studies and eligible clinical trials which are ongoing, but have not been reported yet.

Table 1 summarises the main characteristics and outcomes of the included studies. Two randomised controlled trials were identified. Beigel et al (2020), and Wang et al (2020) examined the impacts of remdesivir in hospitalised patients with COVID-19 and lower respiratory tract disease. A meta-analysis of these two RCTs (Appendix 2), showed no statistically significant difference in all-cause mortality at days 14 to 28 with remdesivir compared to placebo. There was a statistically significant reduction in the incidence of WHO progression score level 6 or above (i.e. requirement for high flow oxygen or mechanical ventilation) at days 14 to 28 compared with placebo (RR 0.76, 95% CI 0.62 to 0.93). Similar results were seen for the incidence of WHO progression score level 7 or above at days 14 to 28 (RR 0.73, 95% CI 0.58 to 0.91). There were statistically significantly fewer serious adverse events in the remdesivir group compared to placebo..

A randomised open-label trial tested shorter and longer duration of treatment with remdesivir in patients with severe Covid-19 not requiring mechanical ventilation (Goldman et al, 2020). The trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir.

One other publication reports the outcomes of a multi-country compassionate-use programme in 61 hospitalised patients. However, it is not possible to draw conclusions from this case series.

The included studies suggest some benefit for remdesivir compared with placebo for time to recovery in severe COVID-19 disease and no significant difference in the rate of adverse events. There were no statistically significant differences in mortality.

Several trials are planned and ongoing with results expected from June 2020. Table 2 describes planned and ongoing trials found during the search.

CONCLUSION

Remdesivir may reduce the time to clinical improvement and prevent disease progression. It is not associated with an increased risk of adverse effects.

The evidence is still quite limitedfor this effect, however. Both RCTS were terminated early – one because of inability to recruit further patients, the other because the Data Safety Monitoring Board felt that the desirable outcomes were already demonstrated, so analyses are underpowered.

The evidence of benefit is small and in selected outcomes only. Remdesivir reduced time to recovery from 15 to 11 days, and resulted in fewer patients progressing to more severe disease (needing ventilation).

Given current limited resources, earlier discharge from hospital and less need for ventilators is desirable.

Adverse events were similar with remdesivir and placebo in the RCTs mentioned above.

Reviewers: Shelley McGee (South African Medical Association), Renee De Waal (Centre for Infectious Disease Epidemiology and Research, University of Cape Town)

Declaration of interests: SM - employed by South African Medical Association that is sponsored by various pharmaceutical and device companies for CPD activities, exhibition at conferences and advertising in SAMJ; RdW - has no interests to declare

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6. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. The New England journal of medicine. 2020.

Table 1. Characteristics of included studies

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Goldman et al 2020 Remdesivir for 5 or 10 Days in Patients with Severe Covid-19(4) https://www.nejm.org/doi/full/10.1056/NEJMoa2015301?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed	Randomised open label phase 3 trial	hospitalized patients > 12 years of age with confirmed SARS-CoV-2 infection. Eligible patients had radiographic evidence of pulmonary infiltrates and either had oxygen saturation of 94% or less while they were breathing ambient air or were receiving supplemental oxygen. N= 200 5-day course of remdesivir N= 197 10-day course.	All the patients were to receive 200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days. The primary efficacy end point was clinical status assessed on day 14 on a 7-point ordinal scale consisting of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring low-flow supplemental oxygen; 5, hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19); 6, hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for Remdesivir administration); and 7, not hospitalized	The treatment groups were balanced in demographic characteristics but not in baseline disease. By day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P = 0.14). In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir.
Beigel et al. 2020 Remdesivir for the Treatment of Covid-19 - Preliminary Report(5) https://www.nejm.org/doi/full/10.1056/NEJMoa2007764?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed 60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1).	Double-blind, multi-centre randomized, placebo-controlled trial	Adults hospitalized with Covid-19 with lower respiratory tract involvement. n= 541 remdesivir n= 522 placebo At time of treatment initiation: 89% had severe disease. 127 did not require oxygen 421 required oxygen but no ventilation 197 were receiving non-invasive ventilation 272 were receiving invasive ventilation	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2-10 or until discharge/death. Other treatment were allowed if the hospital had included them in a written policy. Other treatment received (if any) wasn't reported. Follow up of 29 days. *Primary outcome:* Time to recovery, defined by either discharge from the hospital (with or without need for home oxygen) or hospitalisation for infection-control purposes only (i.e.no need for oxygen or treatment). *Key secondary outcomes:* • Mortality at days 14 and 28 • Difference in clinical status defined by 8-category scale at day 15 • Grade 3 and 4 adverse events • Serious adverse events	The data and safety monitoring board recommended that the prelimary results presented here be made available before completion of the study. Treating doctors could then request unblinding of their patients' treatment assignment, and switch patients to active treatment at their discretion. At the time of the DSMB review, 132 in the remdesivir group, and 169 in the placebo group had not recovered and had not had their Day 29 visit. Time to recovery: Median recovery time was 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received remdesivir or placebo respectively (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). In a planned sub-group analysis, the reduction in time to recovery was significant only in the group who received oxygen, but no ventilation, at time of remdesivir initiation. Mortality by Day 14: 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04).

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				Serious adverse events were reported for 114 of the 541 patients in the remdesivir group (21.1%) and 141 of the 522 patients in the placebo group (27.0%).
Wang et al (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31022-9.pdf 10 hospitals in China were involved	Double-blind, multi-centre randomised, placebo-controlled trial	Adults hospitalized with SARS-CoV-2 infection, with an interval from symptom onset to enrolment of ≤12 days, oxygen saturation of ≤94% or on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300 mm Hg Remdesivir group (n=158) Placebo group (n=78) *At time of treatment initiation:* 3 did not require oxygen 194 required oxygen but no ventilation 37 were receiving non-invasive ventilation 1 was receiving invasive ventilation	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10 Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. *Primary outcome:* The primary endpoint was time to clinical improvement within 28 days. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or discharge from the hospital, whichever came first. *Secondary outcomes:* Proportions of patients in each category of the six-point scale at day 7, 14, and 28 after randomisation; all-cause mortality at day 28; frequency of invasive mechanical ventilation; duration of oxygen therapy; duration of hospital admission; and proportion of patients with nosocomial infection. *Safety outcomes* included treatment-emergent adverse events, serious adverse events, and premature discontinuations of study drug.	Recruitment was terminated early because of control of the epidemic in Wuhan (the intended sample size was ±450). Time to clinical improvement: median 21·0 days (IQR 13·0 to 28·0) in the remdesivir group vs 23·0 days (IQR 15·0 to 28·0) in the placebo group; HR 1·23 [95% CI 0·87 to 1·75]; In patients with symptom duration of 10 days or less: hazard ratio 1.52 (95% CI 0·95 to 2·43). Clinical improvement rates at days 14 and day 28 were also not statistically significantly different between the groups. 28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]). No significant differences were observed between the two groups in terms of length of mechanical ventilation, length of oxygen support, length of hospital stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28 . Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early
Cochrane 2020 Rapid meta-analysis of Remdesivir versus placebo https://covid-nma.com/living_data/index.php	Meta-analysis of two studies (Beigel et al 2020 and Wang et al 2020)	As for RCTs	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10	See Appendix 2
Published, peer reviewed Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, et al(3)	Compassionate use cohort in multiple centres.	n=61 received compassionate-use remdesivir. Results reported for 53. (7 patients had missing 'post-	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10 No comparator	Median duration of follow up after first dose of remdesivir was 18 days (IQR 13 to 23).

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 Apr 10. doi: 10.1056/NEJMoa2007016 [Epub ahead of print]		baseline information' and 1 had an 'erroneous remdesivir start date'.) United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1), and Canada (1). Hospitalised patients who had confirmed SARS-CoV-2 infection and either an oxygen saturation of 94% or less while breathing ambient air or a need for oxygen support. Patients with kidney or liver impairment, were excluded. At the time of remdesivir initiation 34 (64%) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving ECMO.	Follow up of 28 days	Mortality: 7/53 patients died: 6/34 ventilated patients, and 1/19 patients on oxygen Adverse events: 32/53 had adverse events. 12/53 had serious adverse events (most common: multiple organ-dysfunction, septic shock, acute kidney injury, hypotension). Duration of respiratory support, duration of hospitalisation, and ICU stay were not reported – by the end of follow-up 21 patients were still admitted to hospital. The main outcome reported in the study was change in oxygen support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, non-invasive positive pressure ventilation, invasive mechanical ventilation, extracorporeal membrane oxygenation): '36 of 53 patients (68%) showed an improvement in the category of oxygen support, whereas 8 of 53 patients (15%) showed worsening.'

Table 2. Characteristics of planned and ongoing studies

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
SOLIDARITY trial https://www.ncbi.nlm.nih.gov/pubmed/32242116	Open-label randomized multi-country clinical trial	COVID-19 patients hospitalised with severe illness	Local standard of care alone, OR local standard of care plus one of • Remdesivir (daily infusion for 10 days) • Chloroquine or hydroxychloroquine (oral loading dose, then orally twice daily for 10 days) • Lopinavir + Ritonavir (orally twice daily for 10 days) • Lopinavir + Ritonavir (as above) plus Interferon (daily injection for 10 days).
Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections (REMDECO-19) Sponsor: Assistance Publique - Hôpitaux de Paris https://clinicaltrials.gov/ct2/show/NCT04365725	Retrospective cohort trial to assess the efficacy of remdesivir in hospitalised COVID-19 adults	200 COVID-19 patients hospitalized in several French hospitals	Compassionate use Remdesivir
Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN) https://clinicaltrials.gov/ct2/show/NCT04431453	A Phase 2/3 Single-Arm, Open-Label Study	Following paediatric participants will be enrolled: • *Paediatric participants ≥28 days to <18 years old:* Cohort 1: ≥12 years to <18 years and weight ≥40 kg Cohort 2: ≥28 days to <18 years and weight ≥20 kg to <40 kg Cohort 3: ≥28 days to <18 years and weight ≥12 kg to <20 kg Cohort 4: ≥28 days to <18 years and weight ≥3 kg to <12 kg • *Term neonatal participants 0 days to <28 days old:* Cohort 5: ≥14 days to <28 days of age, gestational age >37 weeks and weight at screening ≥2.5 kg Cohort 6: 0 days to <14 days of age, gestational age >37 weeks and birth weight ≥2.5 kg • *Preterm neonates and infants 0 days to <56 days old:* Cohort 7: 0 days to <56 days of age, gestational age ≤37 weeks and birth weight ≥1.5 kg	Experimental: Remdesivir (RDV) Participants will receive RDV up to 10 days. The RDV dose administered in each cohort is as follows: Cohort 1: intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg daily Cohorts 2-5: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily Cohorts 6-7: IV RDV at a dose to be determined based on RDV exposure data from Cohort 5
Study of Merimepodib in Combination With Remdesivir in Adult Patients With Advanced COVID-19 Sponsor: ViralClear Pharmaceuticals, Inc. https://clinicaltrials.gov/ct2/show/NCT04410354	This phase 2 randomized, double-blind, placebo-controlled study	Approximately 40 adult patients with advanced COVID-19 disease, who have a score of 3 or 4 on the National Institute of Allergy and Infectious Disease (NIAID) 8-point ordinal scale and at least one of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion or symptoms of severe lower respiratory symptoms. Patients will be randomized 1:1 to receive oral administration of MMPD + remdesivir or placebo + remdesivir.	Drug: Merimepodib 400 mg (total daily dose of 1200 mg) for 10 days Other Name: VX-497 Drug: Remdesivir 200 mg loading dose on Day 0 followed by 100 mg daily dose for 4 days. If a subject does not demonstrate clinical improvement, 100 mg daily dose may be extended for up to 5 additional days (for a total of up to 10 days) Placebo Comparator: Placebo + remdesivir Drug: Matching Placebo 0 mg (total daily dose of 0 mg) for 10 days Drug: Remdesivir 200 mg loading dose on Day 0 followed by 100 mg daily dose for 4 days. If a subject does not demonstrate clinical improvement, 100 mg daily dose may be extended for up to 5 additional days (for a total of up to 10 days)

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) Sponsor: Gilead Sciences Information provided by (Responsible Party): Gilead Sciences https://clinicaltrials.gov/ct2/show/NCT04292899	Phase 3 Randomized Open-label Study Estimated completion: June 2020	Patients with severe COVID-19 disease and hospitalised. Aged ≥18 years (at all sites), or aged ≥12 and <18 years of age weighing ≥40 kg. Peripheral capillary oxygen saturation (SpO2) ≤94% or requiring supplemental oxygen at screening.	*There are four study arms.* In each remdesivir is the active, standard of care is the control. Experimental Study arms: **Part A:** Remdesivir (RDV), 5 Days (Not Mechanically Ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5. **Part A:** Remdesivir, 10 Days (Not Mechanically Ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10. **Part B:** Remdesivir, 5 or 10 Days (Extension) Will enroll participants after enrollment to Part A is complete. Participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2-10. **Part B**: Remdesivir 10 days (Mechanically Ventilated) Participants on mechanical ventilation will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2-10
A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA) Sponsor: Hoffmann-La Roche Collaborator: Gilead Sciences https://clinicaltrials.gov/ct2/show/NCT04409262	Phase III, Randomized, Double-Blind, Multicenter Study	Hospitalized with COVID-19 pneumonia confirmed per a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan. Requiring more than 6 L/min supplemental oxygen to maintain SpO2 > 93%.	Experimental: Remdesivir + Tocilizumab (RDV+TCZ) RDV loading dose followed by one infusion of TCZ on Day 1, and a once-daily maintenance dose of remdesivir from Days 2-10. Active Comparator: Remdesivir + Placebo (RDV+Placebo) Patients assigned to the RDV + placebo arm will receive an RDV loading dose followed by one infusion of TCZ-placebo on Day 1, and a once-daily maintenance dose of RDV from Days 2-10.
Adaptive COVID-19 Treatment Trial (ACTT) Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) Information provided by (Responsible Party): National Institute of Allergy and Infectious Diseases (NIAID) https://clinicaltrials.gov/ct2/show/record/NCT04280705	Multicenter, Adaptive, blinded RCT Preliminary results of this study have already been published as per table 1. Final data collection date is set at April 1, 2023	Adults hospitalised with confirmed COVID-19 infection. Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), *OR* Clinical assessment (evidence of rales/crackles on exam) AND SpO2 < / = 94% on room air, *OR* Requiring supplemental oxygen, *OR* Requiring mechanical ventilation.	*Placebo* 200 mg of remdesivir placebo administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir placebo for the duration of the hospitalization up to a 10 days total course. n=220. *Intervention: Other: Placebo* *Intervention: Drug: Remdesivir* 200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir for the duration of the hospitalization up to a 10 days total course. n=220.
Adaptive COVID-19 Treatment Trial 2 (ACTT-II) Sponsor:	Adaptive randomized double-blind	Adults (>=18 ears) admitted to a hospital with symptoms suggestive of COVID-19. Has laboratory-confirmed SARS-CoV-2 AND progressive disease suggestive of ongoing SARS-CoV-2 infection.	*Experimental: Remdesivir plus Baricitinib* 200 mg remdesivir administered IV on Day 1, followed by a 100 mg/day maintenance dose while hospitalised for up to a 10-day total course and 4 mg

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
National Institute of Allergy and Infectious Diseases (NIAID) https://clinicaltrials.gov/ct2/show/NCT04401579	placebo-controlled trial Expected Completion date August 2023	Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR SpO2 < / = 94% on room air, OR Requiring supplemental oxygen, OR Requiring mechanical ventilation or ECMO.	(2 tablets of 2 mg) of Baricitinib administered orally daily for the duration of the hospitalization up to a 14-day total course. *Placebo Comparator: Remdesivir plus Placebo* 200 mg remdesivir administered IV on Day 1, followed by a 100 mg/day maintenance dose of Remdesivir while hospitalised for up to a 10-day total course and 4 mg (2 tablets of 2 mg) of baricitinib placebo administered orally daily for the duration of the hospitalisation up to a 14-day total course.
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients Sponsor: Oslo University Hospital Information provided by (Responsible Party): Andreas Barratt-Due, Oslo University Hospital https://clinicaltrials.gov/ct2/show/NCT04321616	The WHO NOR-(Coronavirus infectious disease) COVID 19 multi-centre, adaptive, randomised, open clinical trial	Adult patients, Confirmed SARS-2-CoV-2 infection by PCR Admitted to the hospital ward or the ICU	*Drug: Hydroxychloroquine:* Orally (in ICU via gastrointestinal tubes) with 800 mg x 2 loading dose followed by 400 mg x 2 every day for a total of 10 days. *Drug: Remdesivir* Given intravenously 100 mg daily for the duration of the hospitalization and up to 10 days total course, with a loading dose of 200 mg at inclusion. *Other: Standard of Care* Supplied to all patients not receiving a drug intervention.
Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) Sponsor: Institut National de la Santé Et de la Recherche Médicale, France Information provided by (Responsible Party): Institut National de la Santé Et de la Recherche Médicale, France https://clinicaltrials.gov/ct2/show/NCT04315948	Multi-centre, adaptive, randomized, open clinical trial	Adult patients with laboratory-confirmed SARS-CoV-2 infection. Hospitalized patients with illness of any duration, and at least one of the following: Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR Acute respiratory failure requiring mechanical ventilation and/or supplemental oxygen.	*Remdesivir:* 200 mg IV loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalisation up to a 10 days total course; n=620 *Lopinavir/ritonavir:* 400/100 mg administered every 12 h for 14 days in tablet form. Patients unable to take medications by mouth, the lopinavir/ritonavir will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube; n=620 *Experimental: Lopinavir/ritonavir plus Interferon ß-1a:* 400 lopinavir mg/100 mg ritonavir administered every 12 h for 14 days in tablet form. Patients unable to take medications by mouth, the lopinavir/ritonavir will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube; n=620. Interferon ß1a administered subcutaneously at the dose of 44 µg for a total of 3 doses in 6 days (day 1, day 3, day 6); n=620 *Experimental: Hydroxychloroquine:* Oral loading dose of 400 mg twice daily for one day followed by 400 mg/day for 9 days. The loading dose of hydroxychloroquine through a nasogastric tube will be increased to 600 mg twice a day for one day, followed by a maintenance dose of 400 mg/day for 9 days; n=620

Appendix 1: Search strategy

PubMed ((coronavirus[title/abstract] or covid*[title/abstract] or 2019-ncov[title/abstract] or sars-cov-2[title/abstract])) and (remdesevir[title/abstract] or remdesivir*[title/abstract]) not ((animals[mh] not humans[mh])) And ("2019/12/01"[date - publication] : "3000"[date - publication]) **Output:** 167 records, 7 relevant
ClinicalTrials.Gov Remdesivir **Output**: 35 records, 9 relevant.
Epistemonikos title:(coronavirus OR covid* OR 2019-ncov OR sars-cov-2) OR abstract:(coronavirus OR covid* OR 2019-ncov OR sars-cov-2) AND title:(remdesivir) AND abstract:(remdesivir) **Output 20 records:** 8 after duplicates removed - appropriate to the severe cases
Cochrane Living Synthesis https://www.cochrane.org/news/cochrane-france-leads-collaborative-covid-19-living-evidence-project https://covid-nma.com/living_data/index.php

Appendix 2: Summary of Cochrane Living Meta-analysis: Remdesivir compared to Placebo for Moderate/Severe COVID-19

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Remdesivir			
Incidence of clinical improvement D7	26 per 1.000	**25 per 1.000** (5 to 135)	**RR 0.99** (0.18 to 5.27)	236 (1 RCT)	⊕◯◯◯ VERY LOW
Incidence of clinical improvement D14-D28	577 per 1.000	**652 per 1.000** (525 to 813)	**RR 1.13** (0.91 to 1.41)	236 (1 RCT)	⊕⊕◯◯ LOW
All-cause mortality D7	51 per 1.000	**63 per 1.000** (21 to 195)	**RR 1.23** (0.40 to 3.81)	236 (1 RCT)	⊕⊕◯◯ LOW
All-cause mortality D14-D28	107 per 1.000	**79 per 1.000** (43 to 146)	**RR 0.74** (0.40 to 1.37)	1299 (2 RCTs)	⊕⊕◯◯ LOW
Adverse events D14-D28	641 per 1.000	**660 per 1.000** (538 to 808)	**RR 1.03** (0.84 to 1.26)	233 (1 RCT)	⊕⊕⊕◯ MODERATE
Serious adverse events D14-D28	268 per 1.000	**207 per 1.000** (169 to 252)	**RR 0.77** (0.63 to 0.94)	1296 (2 RCTs)	⊕⊕⊕◯ MODERATE

Appendix 3: Forest plots for Cochrane Living Meta-analysis: Remdesivir compared to Placebo for Moderate/Severe COVID-19

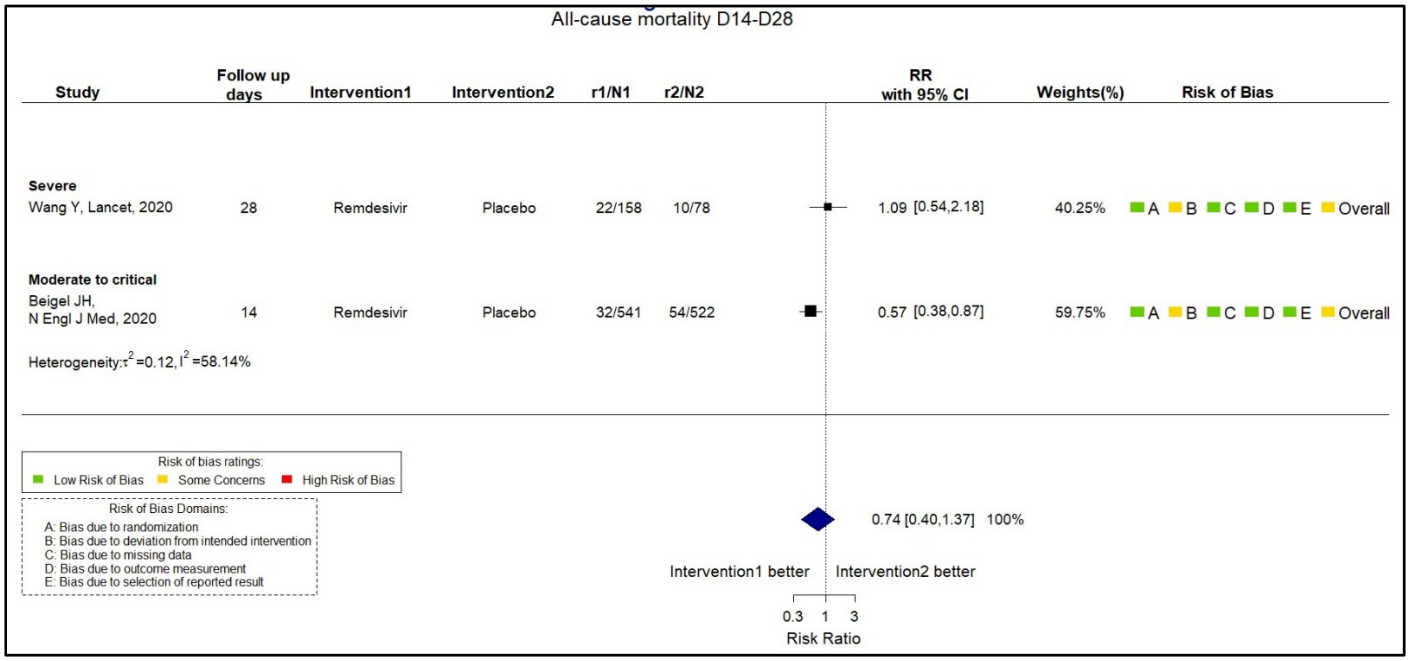

Figure 1: All-cause mortality, D14-28

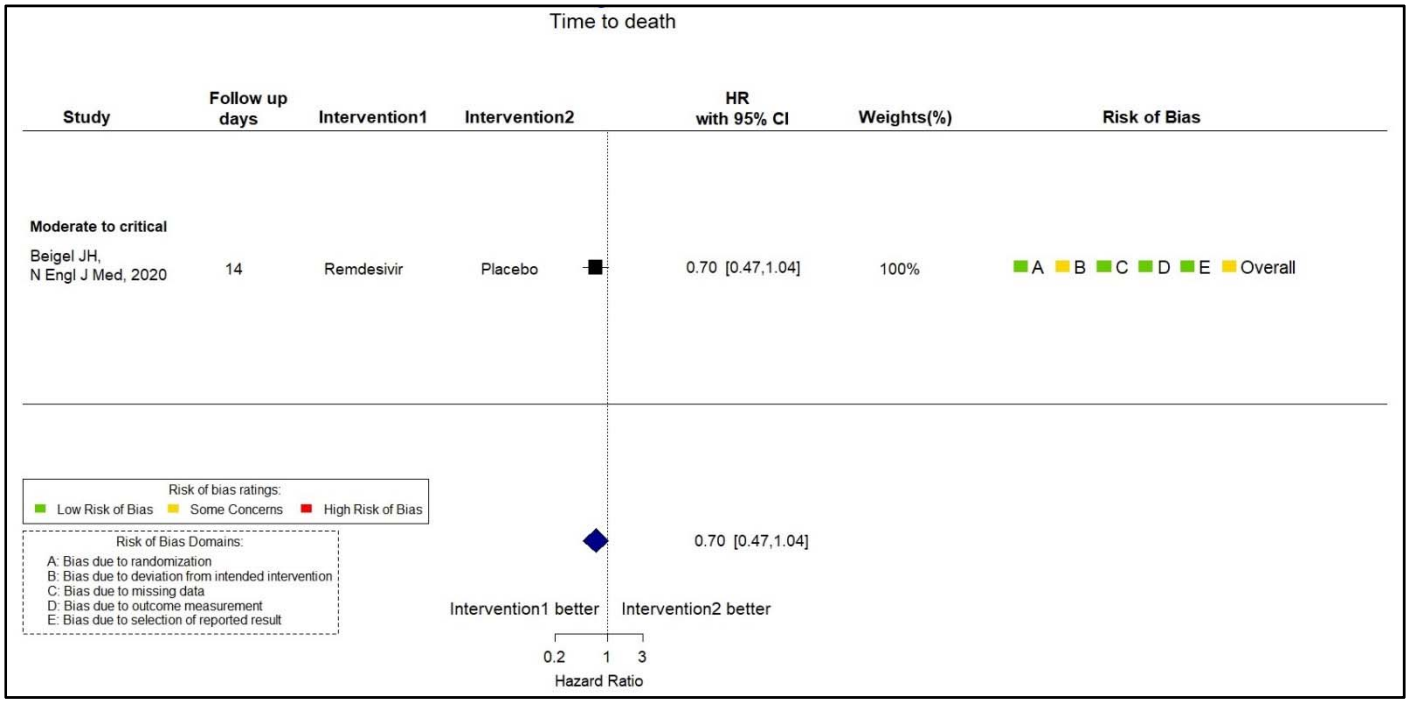

Figure2: Time to death

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [X] Very low: [ ] *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	Two RCTs. Both were terminated early – one because of inability to recruit further patients, the other because further randomisation was considered unnecessary, so analyses are underpowered.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [ ] Moderate: [ ] Small: [x] None: [ ]	There is no impact on mortality (All-cause mortality D14-28: RR 0.74 (0.40 to 1.37)). Remdesivir reduced time to recovery from 15 to 11 days, and resulted in fewer patients progressing to more severe disease (needing ventilation). However, the evidence of benefit is small. Given current limited resources, earlier discharge from hospital and less need for ventilators is desirable.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [x] Low: [ ] Very low: [ ] *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	Adverse events were similar with remdesivir and placebo in the RCTs mentioned above.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [x]	There does not seem to be any additional harms versus placebo.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [x] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
OVERALL QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [X] Very low: [ ] *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	Only two small trials have been published at this point and confidence intervals were relatively wide.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [ ] No: [ ] Uncertain: [X]	Medicine is not SAHPRA registered, but enquiries can be made with the supplier regarding donation-access programme; or may be **accessed via Section 21**. Although emergency use authorisation only has been issued by the US FDA, the EMA has recommended conditional marketing authorisation, on the basis of a rolling review of the emergent evidence: https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-veklury_en.pdf. The approved product information is accessible at: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf SAHPRA registration may be expedited due to the conditional EMA registration.

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td><td>Price of medicines/treatment course:<table><tr><th>Medicine</th><th>Price (ZAR)*</th></tr><tr><td>Remdesivir, IV, 200 mg loading dose, followed by 100 mg per day for 5-10 days (7 to 12 vials)</td><td>5 days: 7438.62 to 16989
10 days: 12751.20 to 29124.00</td></tr></table>*The original manufacturer has licensed a number of Indian generic firms to make generic versions, and has included South Africa in the list of countries to which such products can be exported. Indicative costs for the generic versions, from potential South African supplier(s), is US$55 –US$150 per dose excluding VAT. At an exchange rate of R16.18, a vial would cost R1062.60–R2427.00.
Note: Scale of volume procurement will affect the price.
Reference: Email (29June2020) on file – Official quotation received by NDoH, Affordable Medicines Directorate.

Additional resources: Safety monitoring (liver function tests).</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor:
Major:
Uncertain: X
Is the option acceptable to key stakeholders?
Yes: X
No:
Uncertain:</td><td>Patients: No specific research surveying patients' value of this therapeutic agent is currently available.

Healthcare workers likely consider the intervention to be acceptable.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes:
No:
Uncertain: X</td><td>This would depend on the ability of hospitals to access the medicine via section 21.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
First	16 April 2020	SM, RdW	Currently insufficient evidence to recommend remdesivir in treatment guidelines for COVID-19, except in a clinical trial setting.
Second	24 June 2020	SM, RdW	Remdesivir does not warrant preferential use over other alternative options. While evidence for the efficacy of remdesivir has improved it is still generally weak to moderate. The reduced time to improvement of severe disease may be desirable in the face of limited resources.