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Remdesivir in hospitalised COVID-19 patients

Efficacy and access

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Learning objectives

You will learn:

- In hospitalised patients with severe COVID-19, trial data have shown a significantly shorter recovery time in remdesivir-treated patients but no significant difference in mortality when compared to placebo
- Hospitalised patients with moderate COVID-19 on a five-day course of remdesivir had a statistically significantly better clinical status than those randomised to standard care
- Evidence of remdesivir efficacy, as with many novel treatments for COVID-19-related illnesses, still requires specific answers with regard to aspects such as the optimal patient population, duration of therapy and effect on discrete clinical outcomes
- The South African National Essential Medicine List Committee (NEMLC) COVID-19 Subcommittee currently does not recommend the use of remdesivir for treatment of all hospitalised patients requiring oxygen or ventilation, although the FDA has recently endorsed its wider use
- With COVID-19 expected to be around for the foreseeable future, remdesivir has an important role to play for patients and healthcare providers in easing the burden on the health system, particularly the demand for ICU beds.

Introduction

The experimental antiviral remdesivir, a nucleoside analogue prodrug, has shown promising activity in preclinical models of severe coronavirus infection. Remdesivir has inhibitory effects on pathogenic animal and human coronaviruses in vitro, and inhibits Middle East respiratory syndrome-related coronavirus (MERS), severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), and the virus responsible for the current COVID-19 pandemic, SARS-CoV-2.

Between late January and early March 2020, clinical improvement was observed in 36 of 53 patients (68 %) hospitalised for severe COVID-19 and treated with compassionate-use remdesivir, prompting further studies of the efficacy of remdesivir in the treatment of patients with COVID-19.[1] In May 2020, the United States' Food and Drug Administration (FDA) granted emergency-use authorisation for remdesivir in the treatment of patients hospitalised with severe COVID-19.[2] This decision was informed by the results of the Adaptive COVID-19 Treatment Trial (ACTT-1), which found a shortened recovery time in those assigned remdesivir as compared to placebo.[3] The European Medicines Agency and the Therapeutic Goods Administration of Australia have since given provisional approval for remdesivir, pending additional data on safety and efficacy.

This review considers the clinical evidence for the use of remdesivir in hospitalised patients with severe COVID-19, as well as issues of access in the South African context. Professor Guy Richards contributes his clinical expertise and perspective.

Patients assigned a 10-day course of remdesivir had a recovery time that was shorter by four days, compared with placebo

What is the evidence for the use of remdesivir in hospitalised COVID-19 patients?

Randomised controlled trials (RCTs) comparing remdesivir to standard care (or placebo) in hospitalised patients with moderate to severe COVID-19, and another trial comparing a five-day and 10-day course of remdesivir in hospitalised patients with severe COVID-19 are summarised below.

Remdesivir vs placebo in severe COVID-19

The first of the trials to compare a 10-day course of remdesivir with placebo in hospitalised patients with severe COVID-19 was performed by Wang and colleagues[4] in Hubei, China. This double-blind, placebo-controlled, multicentre trial evaluated the efficacy of remdesivir in patients with severe COVID-19, who were admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94 % on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mmHg, and radiologically confirmed pneumonia. Recruited patients (n = 237) were randomised to intravenous (IV) remdesivir (200 mg on day one, 100 mg on days 2-10) or the same volume of placebo infusions in a 2:1 ratio. The primary endpoint of time to clinical improvement was defined as the time in days from randomisation to the point of a two-level decline on a six-point ordinal scale of clinical status or discharged alive from hospital, whichever came first.

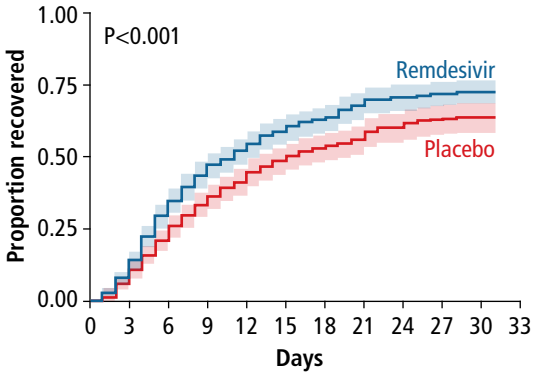
Key findings: In this study, which was underpowered, remdesivir was not associated with statistically significant clinical benefits. However, in a further underpowered subgroup analysis, patients with a symptom duration of ≤ 10 days who received remdesivir had a faster time to clinical improvement than those receiving placebo.

ACTT-1, a subsequent larger study performed by Beigel and colleagues, evaluated the efficacy and safety of remdesivir in patients hospitalised with COVID-19 infection, and evidence of lower respiratory tract infection.[3] In this phase 3, randomised, double-blind, placebo-controlled, multicentre trial, 1 059 patients were randomly assigned (2:1) to remdesivir (n = 538) with an initial loading dose of 200 mg in 350 ml of normal saline on day one and thereafter a daily maintenance dose of 100 mg in 250 ml normal saline for nine days, or placebo (n = 521) with a loading dose 350 ml normal saline and

thereafter a daily maintenance dose of 250 ml normal saline.

Key findings: Patients assigned a 10-day course of remdesivir had a recovery time that was shorter by four days, compared with placebo (Figures 1 and 2). Importantly, no significant difference was found in mortality between remdesivir (7.1 %) and placebo (11.9 %).

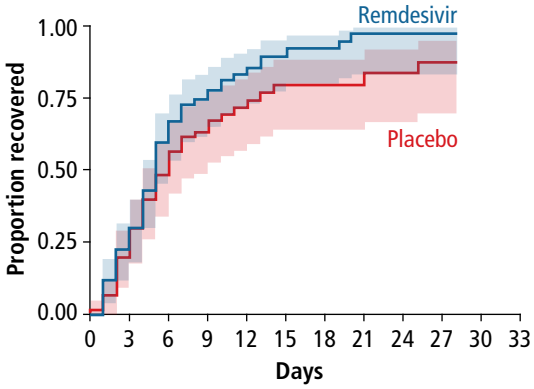
A Overall



No. at risk

Remdesivir	583	481	363	274	183	142	121	98	78	65	3	0
Placebo	521	481	392	307	224	180	149	115	91	78	2	0

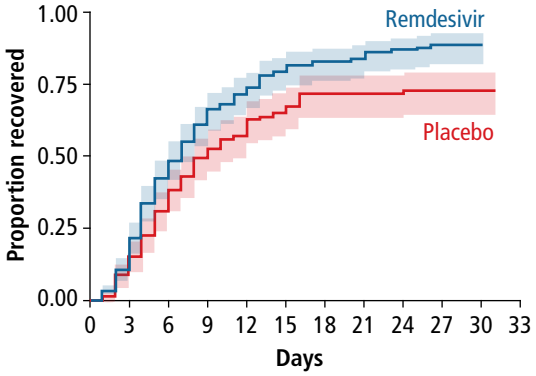
B Patients no receiving oxygen



No. at risk

Remdesivir	67	52	27	16	8	4	3	1	1	1	0	0
Placebo	60	48	31	18	11	7	7	5	4	3	0	0

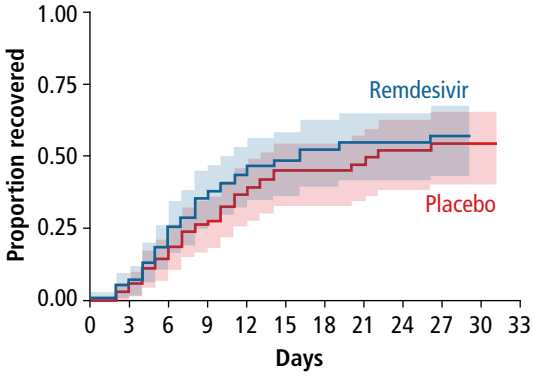
C Patients receiving oxygen



No. at risk

Remdesivir	222	194	124	79	47	30	23	21	15	12	2	0
Placebo	199	179	131	91	61	43	33	29	26	23	1	0

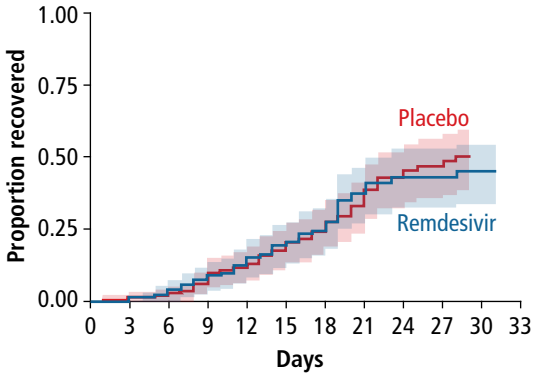
D Patients receiving high-flow oxygen or non-invasive mechanical ventilation



No. at risk

Remdesivir	98	92	77	67	35	27	23	20	19	17	0	0
Placebo	99	96	80	62	47	37	34	23	18	17	1	0

E Patients receiving mechanical ventilation or ECMO



No. at risk

Remdesivir	125	124	120	111	91	80	71	55	42	34	1	0
Placebo	147	145	141	127	102	91	73	56	41	33	0	0

Kaplan-Meier estimates of cumulative recoveries are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not receiving oxygen; Panel B), in those with a baseline score of 5 (receiving oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or non-invasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or ECMO; Panel E).

Figure 1. ACTT-1: remdesivir vs placebo in patients hospitalised with severe COVID-19[3]

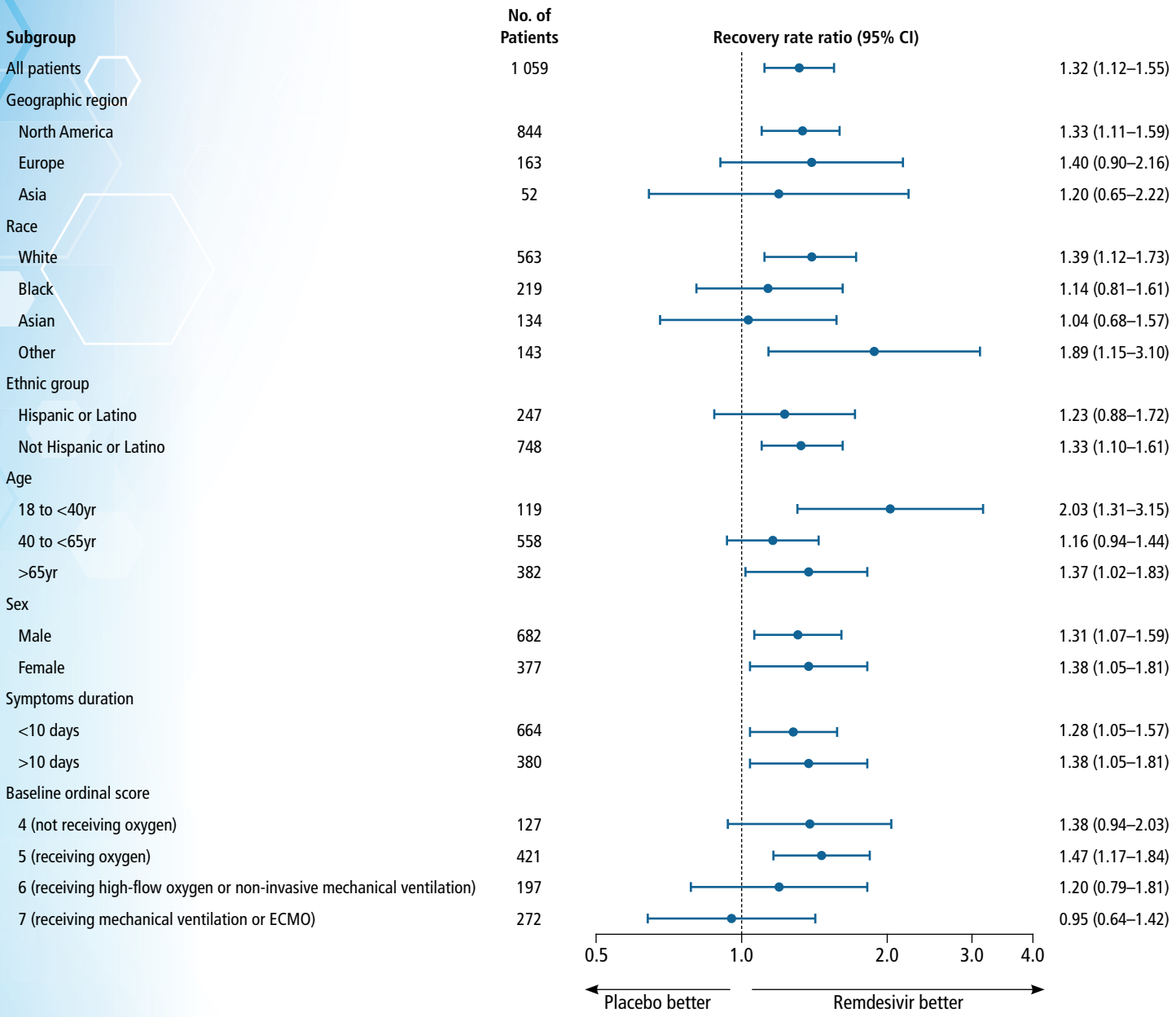


Figure 2. ACTT-1: time to recovery according to subgroup[3]

Remdesivir for 5 or 10 days in patients with severe COVID-19

A clinical improvement of two points or more on the ordinal scale occurred in 64 % of patients in the five-day group and 54 % in the 10-day group

A head-to-head comparison of remdesivir for five or 10 days in hospitalised patients with severe COVID-19 was undertaken by Goldman and colleagues in a randomised, open-label, phase 3 trial.[5] Hospitalised patients (n = 397) with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94 % while breathing ambient air and radiological evidence of pneumonia were randomly assigned 1:1 to receive remdesivir for either five or 10 days, with no placebo control. All patients received 200 mg remdesivir on day one and 100 mg once daily on subsequent days. Median duration of treatment was five days in the five-day group and nine days in the 10-day group. The primary endpoint was clinical status on day 14, assessed on a seven-point ordinal scale. At baseline, patients assigned to the 10-day group had significantly worse clinical status than those assigned to the five-day group (p = 0.02).

Key findings:: A clinical improvement of two points or more on the ordinal scale occurred in 64 % of patients in the five-day group and 54 % in the 10-day group, showing no significant difference between a five-day course and a 10-day course of remdesivir in patients with severe COVID-19 not requiring mechanical ventilation. With no placebo control, however, the magnitude of benefit cannot be determined.

Remdesivir in patients with moderate COVID-19

At 11 days after initiation of treatment, patients randomised to a five-day course of remdesivir had a statistically significantly better clinical status compared with those randomised to standard care

A randomised, open-label, phase 3, multicentre trial by Spinner and colleagues[6] questioned whether remdesivir provides a benefit on clinical status for patients hospitalised with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation > 94 %). The day 11 clinical status distribution of 584 patients who were randomised in a 1:1:1 ratio to a five-day (n = 199) or 10-day (n = 197) course of remdesivir, or standard care (n = 200), was measured on a seven-point ordinal scale. Patients randomised to a five-day course of remdesivir had a median length of treatment of five days and patients randomised to a 10-day course had a median length of treatment of six days, with only 38 % of patients completing the full course. Nausea (10 % vs 3 %), hypokalaemia (6 % vs 2 %), and headache (5 % vs 3 %) were more frequent among remdesivir-treated patients compared to those on standard care.

Key findings: At 11 days after initiation of treatment, patients randomised to the five-day course of remdesivir had a statistically significantly better clinical status compared with those randomised to standard care, but the difference was of uncertain clinical importance. Counterintuitively, the clinical status of those randomised to a 10-day course of remdesivir was not significantly different compared to that of those who received standard care. Of note, there was no difference between either of the remdesivir groups or patients on standard care in any prespecified secondary end-point analysis, which included mortality.

What are important design differences that may influence results across these trials?

Use of an ordinal scale approach is endorsed by the World Health Organization; however the scale is newly created and potentially problematic

With equivocal trial results on the use of remdesivir in hospitalised patients with moderate to severe COVID-19, questions are raised as to whether these discrepancies are due to study design choices, including patient populations, or whether remdesivir is less efficacious than hoped.

Although all the RCTs required evidence of pulmonary involvement as part of the recruitment criteria, the study populations are not the same across the trials. ACTT-1 and the study by Wang and colleagues recruited patients who required supplementary oxygen or ventilatory support, whereas the study by Spinner and colleagues included patients who, at baseline, did not require oxygen.[7]

The trial by Spinner and colleagues was open-label because of an inadequate supply of placebo-containing vials. The authors suggest that clinicians may have inadvertently delayed hospital discharge in the remdesivir group to facilitate completion of the IV treatment course, and also that clinicians may have provided aspects of care that differed between the control and active treatment groups.[7]

Use of an ordinal scale approach is endorsed by the World Health Organization; however the scale is newly created and potentially problematic. Each step on the ordinal scale is not necessarily of equivalent clinical significance and therefore, distribution of clinical status scores may be disproportionate for meaningful interpretation of clinical significance. Furthermore, if the distribution of clinical status scores is not proportional, there is no way to quantify the net benefit of an active agent that may improve scores at one part of the scale but worsen scores elsewhere. A variation of an ordinal scale, ranging from recovery through increasing levels of ongoing hospital care to death, was used by all three RCTs to measure the primary outcome. Wang *et al* used the ordinal scale to measure time to recovery, ACTT-1 and the study by Spinner and colleagues measured the primary study outcome at study day 11.[6,7]

A minority of patients assigned to receive a 10-day course of remdesivir in both ACTT-1 and the trial by Spinner *et al* actually received the 10 full days of therapy, thereby confounding whether it could be inferred that differences in outcome could be due to duration of therapy.[7]

It is important to note that these RCTs concluded enrolment prior to publication of findings from the RECOVERY trial showing that dexamethasone reduced mortality in patients with severe COVID-19, but not in hospitalised patients who did not require

supplemental oxygen. There was no formal cross-randomisation and interrogation of treatment-by-treatment interactions between remdesivir and corticosteroids in the RCTs.[7,8]

Professor Richards interprets the trial results

Despite differences in study design that may account for variation in results of the RCTs, important questions remain regarding the efficacy of remdesivir:[7]

- The optimal patient population has not been elucidated
- The optimal duration of therapy needs clarification
- The effect on discrete clinical outcomes requires further investigation
- The relative effect of remdesivir if given in the presence of dexamethasone or other corticosteroids has not yet been explored; whether remdesivir offers incremental benefit over these corticosteroids remains unknown.

The South African context - adequate, equitable and affordable access

Professor Richards provides insights for the clinician

Remdesivir is best used early in patients with COVID-19 pneumonia and in combination with corticosteroids; treating both the viraemia and the inflammatory response simultaneously is likely to show the most benefit. Delayed treatment of patients, particularly if mechanically ventilated, is unlikely to be of benefit.

Recommendations on the use of remdesivir from the South African National Essential Medicine List Committee (NEMLC) COVID-19 Subcommittee read:[9]

> "**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 a S21 application process. Availability of limited S21 supplies would impact equity.*
>
> **Level of evidence:** *RCTs of low-to-moderate quality."*

Application for Section 21 approval, which has been granted in South Africa, is generally on a per-patient basis, although a specific hospital may be given permission to hold buffer stock of remdesivir and apply per patient after initiation of therapy.

Gilead has licenced nine generics companies in developing countries, including South Africa, to manufacture a generic form of remdesivir. Although in South Africa the generic drug costs seven times less than the original it remains expensive and, furthermore, the initial offering was only enough for 5 000 patients, raising questions about affordability and the ethics of equitable access.

With COVID-19 expected to be around for the foreseeable future, remdesivir has an important role to play for patients, for easing the burden on the health system (particularly demand for ICU beds) and in research. Local research is necessary to determine the efficacy of remdesivir in the South African population, as research to date originates from the USA and Europe, with participants being mostly white males.

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Key learnings

- Compassionate-use remdesivir treatment in patients hospitalised for severe COVID-19 found an observed clinical improvement in 68 % of patients, prompting subsequent RCTs on the efficacy of remdesivir in the treatment of COVID-19
- The ACTT-1 trial of remdesivir in patients hospitalised with severe COVID-19 demonstrated that, compared with placebo, a 10-day course of remdesivir was associated with a recovery time that was four days shorter
- In hospitalised patients with moderate COVID-19, patients randomised to a five-day course of remdesivir had a statistically significant better clinical status at day 11, compared with those randomised to standard care
- Important questions remain regarding the optimal use of remdesivir for the treatment of COVID-19.

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