Annals of Internal Medicine

REVIEW

Major Update 2: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points

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Background: Remdesivir is approved for the treatment of adults hospitalized with COVID-19.

Purpose: To update a living review of remdesivir for adults with COVID-19.

Data Sources: Several electronic U.S. Food and Drug Administration, company, and journal websites from 1 January 2020 through 19 October 2021.

Study Selection: English-language, randomized controlled trials (RCTs) of remdesivir for COVID-19.

Data Extraction: One reviewer abstracted, and a second reviewer verified data. The Cochrane Risk of Bias Tool and GRADE (Grading of Recommendations Assessment, Development and Evaluation) method were used.

Data Synthesis: Since the last update (search date 9 August 2021), 1 new RCT and 1 new subtrial comparing a 10-day course of remdesivir with control (placebo or standard care) were identified. This review summarizes and updates the evidence on the cumulative 5 RCTs and 2 subtrials for this comparison. Our updated results confirm a 10-day course of remdesivir, compared with control, probably results in little to no mortality reduction (5 RCTs). Updated results also confirm that remdesivir probably results in a moderate increase in the proportion of patients recovered by day 29 (4 RCTs) and may reduce time to clinical improvement (2 RCTs) and hospital length of stay (4 RCTs). New RCTs, by increasing the strength of evidence, lead to an updated conclusion that remdesivir probably results in a small reduction in the proportion of patients receiving ventilation or extracorporeal membrane oxygenation at specific follow-up times (4 RCTs). New RCTs also alter the conclusions for harms—remdesivir, compared with control, may lead to a small reduction in serious adverse events but may lead to a small increase in any adverse event.

Limitation: The RCTs differed in definitions of COVID-19 severity and outcomes reported.

Conclusion: In hospitalized adults with COVID-19, the findings confirm that remdesivir probably results in little to no difference in mortality and increases the proportion of patients recovered. Remdesivir may reduce time to clinical improvement and may lead to small reductions in serious adverse events but may result in a small increase in any adverse event.

Primary Funding Source: U.S. Department of Veterans Affairs.

Ann Intern Med. doi:10.7326/M21-4784 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 March 2022.

This is the fifth update of our living, rapid review on remdesivir for adults with COVID-19 (1). Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA (2), is approved by the U.S. Food and Drug Administration for the treatment of adults hospitalized with COVID-19 (3). Our first update, which included randomized controlled trials (RCTs) published through 7 December 2020 (4–8), led to a major update (9). Our second update, including RCTs published through 8 February 2021, found no new evidence (10). Our third update (11) derived from RCTs published through 10 May 2021 included 1 new RCT (12), and our fourth update of RCTs published through 9 August 2021 (13) included 1 new add-on subtrial of the World Health Organization (WHO) Solidarity trial–the Norwegian Solidarity trial (14). On the basis of the results from these RCTs, we had previously concluded that a 10-day course of remdesivir probably results in little to no difference in mortality but probably reduces serious adverse events and may reduce time to recovery in hospitalized patients. Two RCTs found that a 10-day course was not more effective than a 5-day course for moderate and severe disease (6, 7).

This fifth quarterly update including RCTs published through 19 October 2021 is the final update for this living review according to the preplanned protocol. It summarizes information on remdesivir from 2 newly published RCTs by Ader and colleagues (DisCoVeRy [Trial of Treatments for COVID-19 in Hospitalized Adults]; subtrial) (15) and Abd-Elsalam and colleagues (16) alongside previous updates. We update previous analyses and certainty of evidence (COE) and conduct cumulative meta-analyses, where feasible. In addition, we report on results of SARS-CoV-2 clearance.

METHODS

We included RCTs evaluating remdesivir for adults with COVID-19 using methods identical to those described previously (1, 9). Our literature search was updated to

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include RCTs published through 19 October 2021 and used the original search strategies and inclusion criteria (**Supplement Table 1**, available at Annals.org). DisCoVeRy (15) is a subtrial of Solidarity. Results on some patients were also included in the published Solidarity report (8). Hence, for outcomes that were reported by both DisCoVeRy and Solidarity (mortality and new need for ventilation), we did not include DisCoVeRy data in our main analyses to avoid double counting persons. The DisCoVeRy authors provided us data for DisCoVeRy participants who were not previously included in published Solidarity results for these end points (Mentré F. Personal communication.). We used these unpublished data to conduct sensitivity analyses. For outcomes not reported in Solidarity (proportion recovered, proportion on ventilation at follow-up, and adverse events), we included data of all DisCoVeRy patients in our main analyses. Tools to assess risk of bias (17) and estimate COE (18) were unchanged (**Supplement Tables 2 and 9**, available at Annals.org). The definitions of our a priori–defined outcomes, both critical (mortality, proportion recovered, hospital length of stay, and serious adverse events) and important (time to clinical improvement, need for ventilation or extracorporeal membrane oxygenation [ECMO], and any adverse event) and our a priori–established thresholds for estimating effect magnitude for these outcomes were also unchanged (**Appendix Table**, footnote) (1).

Data Synthesis and Analysis

We conducted a cumulative meta-analysis combining data from previous updates with data from the newly identified RCTs when outcomes were reported in at least 3 trials and calculated relative and absolute measures of effect with corresponding 95% CIs. We used a fixed-effects model when outcomes were reported by fewer than 5 trials and a random-effects model (Hartung–Knapp–Sidik–Jonkman) when 5 or more trials reported on the outcome. Data were analyzed in R (R Foundation) (19). The magnitude of statistical heterogeneity was assessed with the I^2 statistic ($I^2 > 75\%$ may indicate substantial heterogeneity) (20).

We include updated meta-analyses, incorporating data from the newly published RCTs for the outcomes of mortality (all severity COVID-19), proportion recovered, proportion receiving mechanical ventilation at follow-up, serious adverse events, and any adverse event. We describe findings for SARS-CoV-2 clearance. Although this outcome was deemed an intermediate, nonclinical outcome, we include this information to address uncertainty about the effect of remdesivir on viral clearance and the potential implications on use of remdesivir on the basis of COVID-19 symptom duration.

Role of the Funding Source

This work is based on a living, rapid review done for the U.S. Department of Veterans Affairs (VA) Evidence Synthesis Program that concludes with this update (21). Funding for that review was provided by the Veterans Health Administration Office of Research and Development, Health Services Research and Development Service. The funding source assigned the topic but was not involved in data collection, analysis, manuscript preparation, or submission.

RESULTS

The updated literature search identified 426 citations (**Appendix Figure**, available at Annals.org). We identified 2 new eligible publications: a subtrial by Ader and colleagues (DisCoVeRy) (15) and an RCT by Abd-Elsalam and colleagues (16). When added to the previous update that includes 6 RCTs and a subtrial, there are a total of 7 RCTs and 2 subtrials that assess effectiveness of remdesivir for COVID-19 (4–8, 12, 14–16).

Overview of All Randomized Trials (9 Trials)

Of the 7 RCTs and 2 subtrials evaluating remdesivir for COVID-19, the 2 new studies (1 RCT and 1 subtrial) add to the previous 5 studies (4 RCTs and 1 subtrial) comparing a 10-day course of remdesivir with control (placebo or standard care [SC]) (4, 5, 8, 14–16). Hence, our updated analyses focus on the 5 RCTs and 2 subtrials comparing a 10-day course of remdesivir with control (4, 5, 7, 8, 14–16). The remaining comparisons between 5-day course and either a 10-day course and/or SC (6, 7) did not have any new evidence. The previous summaries and conclusions from these are presented in summary tables. Details about study characteristics, outcomes, and harms are reported in **Supplement Tables 3 to 8** (available at Annals.org), and information on risk of bias is presented in **Supplement Table 9** (available at Annals.org).

New Findings From Ader and Colleagues (DisCoVeRy) and Abd-Elsalam and Colleagues

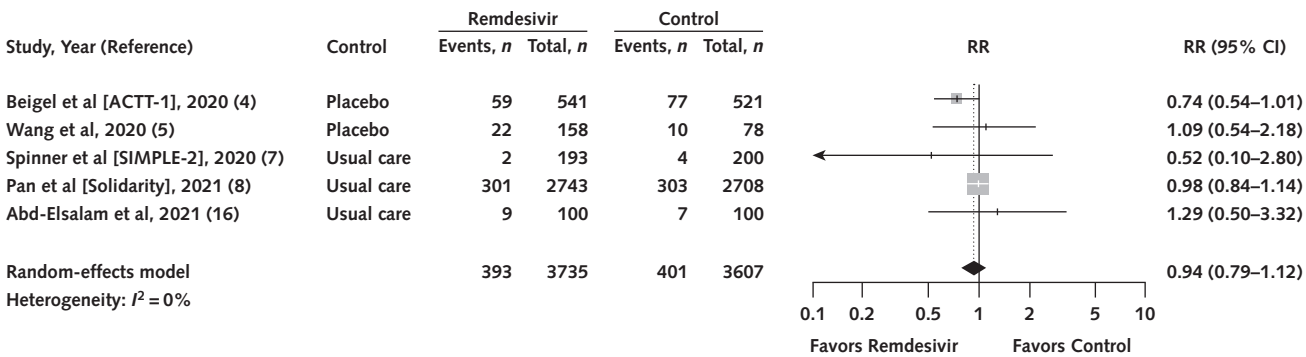
Ader and Colleagues (DisCoVeRy)

DisCoVeRy was a multicenter, open-label subtrial of Solidarity (15) done in Europe (**Supplement Table 3**). DisCoVeRy ($n = 832$) compared a 10-day course of remdesivir with SC for adults hospitalized with laboratory-confirmed COVID-19 with clinical hypoxia or need for oxygen supplementation (**Supplement Table 10**, available at Annals.org). Results from some DisCoVeRy participants (53%) had been included in the published Solidarity report (8). The primary outcome for the DisCoVeRy trial was clinical status at day 15 measured using the WHO 7-point ordinal scale, an outcome not reported in the Solidarity trial. Median symptom duration was 9 days. At baseline, nearly all patients were receiving at least supplemental oxygen, and 40% were receiving corticosteroids. Compared with SC, remdesivir did not result in a statistically significant improvement in clinical status on day 15 (odds ratio, 0.98 [95% CI, 0.77 to 1.25]). In addition, there was no statistically significant difference between remdesivir and SC in time to improvement, length of hospitalization, proportion needing ventilation on day 15, 28-day mortality, serious adverse events, or any adverse events. There was no effect of remdesivir on SARS-CoV-2 kinetics measured in the nasopharynx.

Abd-Elsalam and Colleagues

The study by Abd-Elsalam and colleagues was an open-label RCT done in Egypt (**Supplement Table 3**) (16). The study ($n = 200$) compared a 10-day course of remdesivir with SC for adults hospitalized with laboratory-confirmed COVID-19. The primary outcomes were length of hospital stay and mortality. The median symptom duration and patient stratification by baseline oxygen requirements

Figure 1. Mortality for remdesivir 10-day course versus control (placebo or standard care).



ACTT-1 = Adaptive COVID-19 Treatment Trial; RR = risk ratio; SIMPLE-2 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir [GS-5734] in Participants With Moderate Coronavirus Disease [COVID-19] Compared to Standard of Care Treatment.

were not reported. However, the mean baseline oxygen saturation, reported as 88.5%, was consistent with the National Institutes of Health and WHO definition of severe COVID-19 (Supplement Table 10). Remdesivir, compared with SC, resulted in a statistically significant reduction in median duration of hospitalization (10 vs. 16 days; $P < 0.001$) but did not reduce mortality (9% vs. 7%; $P = 0.602$). Remdesivir did not affect new need for ventilation. No serious adverse events were noted in either group.

Summary Findings

For summary findings, see Figures 1 and 2, the Table, the Appendix Table, and Supplement Tables 1 to 10.

Remdesivir 10-Day Course Compared With Control (Placebo or SC) (7 Trials)

Of the 5 trials and 2 subtrials comparing a 10-day course of remdesivir with control, 2 used a placebo (4, 5) and 5 used SC as the control (7, 8, 14–16) (Supplement Table 3). Five RCTs included patients with severe and critical COVID-19 (4, 5, 8, 14, 15), 1 RCT included only patients with moderate disease (7), and 1 RCT included patients with unclear severity of disease (16). Six studies had a low risk of bias (4, 5, 7, 14–16), and 1 had a moderate risk of bias (8).

All-Cause Mortality

Our updated analyses, including new results from Abd-Elsalam and colleagues (16), confirm that remdesivir compared with control (placebo or SC) probably results in little to no difference in mortality (absolute risk difference [ARD], −0.7% [CI, −2.4% to 1.0%]) (moderate COE) (4, 5, 7, 8, 16) (Figure 1). A sensitivity analysis, with the addition of the results from the 392 patients from DisCoVeRy that were not previously included in the published Solidarity report, produced results similar to those of the primary analysis. Prior subgroup analyses for mortality by baseline oxygen support requirements remain unchanged (9) because the newly included RCT (16) did not stratify patients by baseline disease severity or oxygen needs.

Proportion of Patients Recovered

Updated analyses, including new results from DisCoVeRy (15), confirm that remdesivir, compared with control, probably results in a moderate increase in the percentage of patients who recovered by day 28 or 29 (ARD, 6.5% [CI, 3% to 10%]) (moderate COE) (4, 5, 7, 15) (Figure 2, *A*). Recovery was defined as not hospitalized (15), discharged from the hospital or hospitalization for infection control purposes only (4), or discharged from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (5, 7).

Proportion with Clinical Improvement

No new studies provided data on this outcome. Hence, our prior conclusion that remdesivir, compared with control, may result in a moderate increase in the proportion with clinical improvement by day 28 is unchanged (range of ARDs, 7.2% to 7.5%; 2 RCTs) (low COE) (5, 7).

Hospital Length of Stay

Updated analyses, including results from 2 new studies versus SC—DisCoVeRy and Abd-Elsalam and colleagues (15, 16)—show that remdesivir may result in up to a moderate reduction in hospital length of stay compared with control (low COE) (4, 5, 15, 16).

Percentage of Patients Hospitalized

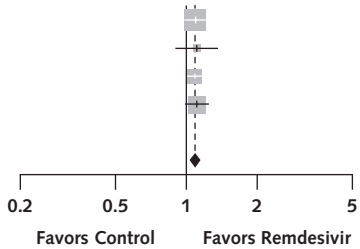
No new studies provided data on this outcome. Our prior conclusion that remdesivir, compared with control, may not decrease the percentage of patients hospitalized between days 7 and 14 is unchanged (2 RCTs) (low COE) (7, 8).

Time to Recovery

No new studies provided data on this outcome. Our prior conclusion that remdesivir, compared with control, may result in a large reduction in patients with severe disease and an uncertain reduction in time to recovery in patients with moderate disease remains unchanged (2 RCTs) (low COE) (4, 7).

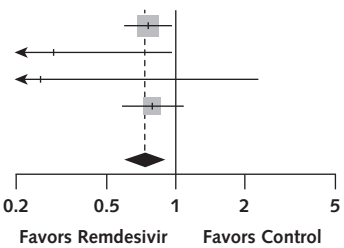
Figure 2. Nonmortality outcomes for remdesivir 10-day course versus control (placebo or standard care).

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Beigel et al [ACTT-1], 2020 (4)	Placebo	399	541	352	521	1.09 (1.01–1.18)
Wang et al, 2020 (5)	Placebo	106	150	49	77	1.11 (0.91–1.35)
Spinner et al [SIMPLE-2], 2020 (7)	Usual care	178	193	170	200	1.09 (1.01–1.17)
Ader et al [DisCoVeRy], 2021 (15)	Usual care	265	414	241	418	1.11 (1.00–1.24)
Fixed-effects model		948	1298	812	1216	1.10 (1.04–1.15)
Heterogeneity: $I^2 = 0\%$						



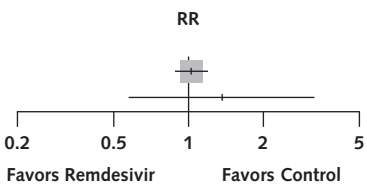
Proportion receiving ventilation or ECMO at follow-up (assessed on day 11, 14, or 15)

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Beigel et al [ACTT-1], 2020 (4)	Placebo	95	541	121	521	0.76 (0.59–0.96)
Wang et al, 2020 (5)	Placebo	4	153	7	78	0.29 (0.09–0.97)
Spinner et al [SIMPLE-2], 2020 (7)	Usual care	1	193	4	200	0.26 (0.03–2.30)
Ader et al [DisCoVeRy], 2021 (15)	Usual care	62	414	79	418	0.79 (0.58–1.07)
Fixed-effects model		162	1301	211	1217	0.74 (0.62–0.89)
Heterogeneity: $I^2 = 13\%$						

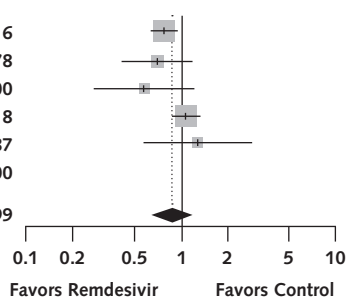


New need for ventilation or ECMO (within 28 d or 6 mo)

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Pan et al [Solidarity], 2021 (8)	Usual care	295	2489	284	2475	1.03 (0.89–1.20)
Abd-Elsalam et al, 2021 (16)	Usual care	11	100	8	100	1.38 (0.58–3.27)



Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Seigel et al [ACTT-1], 2020 (4)	Placebo	131	532	163	516	0.78 (0.64–0.95)
Wang et al, 2020 (5)	Placebo	28	155	20	78	0.70 (0.43–1.17)
Spinner et al [SIMPLE-2], 2020 (7)	Usual care	10	193	18	200	0.58 (0.27–1.22)
Ader et al [DisCoVeRy], 2021 (15)	Usual care	135	406	130	418	1.07 (0.88–1.30)
Barratt-Due et al [NOR-Solidarity], 2021 (14)	Usual care	8	42	13	87	1.27 (0.57–2.84)
Abd-Elsalam et al, 2021 (16)	Usual care	0	100	0	100	
Random-effects model		312	1428	344	1399	0.87 (0.64–1.18)
Heterogeneity: $I^2 = 50\%$						



ACTT-1 = Adaptive COVID-19 Treatment Trial; DisCoVeRy = Trial of Treatments for COVID-19 in Hospitalized Adults; ECMO = extracorporeal membrane oxygenation; RR = risk ratio; SIMPLE-2 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir [GS-5734] in Participants With Moderate Coronavirus Disease [COVID-19] Compared to Standard of Care Treatment. **Top.** Proportion recovered. **Middle.** Need for invasive ventilation or ECMO. **Bottom.** Patients with ≥1 serious adverse events.

Table. Summary of Conclusions and Updated Findings for Randomized Trials of Remdesivir

Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
Remdesivir 10-d course vs. control (placebo or SC) for any severity of COVID-19; 5 trials and 2 subtrials (*n* = 7772 unique patients randomly assigned) (4, 5, 7, 8, 14, 15, 16)			
Mortality	Remdesivir 10-d course probably results in little to no difference vs. control	1 new RCT (16) vs. SC	Updated results confirm remdesivir 10-d course probably results in little to no difference vs. control (4, 5, 7, 8, 16)
Proportion recovered*	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. control	Results from 1 subtrial vs. SC (15)	Updated results confirm remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. control (4, 5, 7, 15)
Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase in percentage with clinical improvement vs. control (5, 7)	No new evidence	No change in conclusions
Hospital length of stay	Remdesivir 10-d course may result in up to a moderate reduction in hospital length of stay vs. control	1 new RCT (16) and results from 1 subtrial (15), both vs. SC	Updated results confirm remdesivir 10-d course may result in up to a moderate reduction in hospital length of stay vs. control (4, 5, 15, 16)
Time to recovery	Remdesivir 10-d course may result in a large reduction in time to recovery in patients with severe disease and an uncertain reduction for patients with moderate disease vs. control (4, 7)	No new evidence	No change in conclusions
Time to clinical improvement	Remdesivir 10-d course may result in a small reduction in time to clinical improvement vs. control	Results from 1 subtrial vs. SC (15)	Updated results confirm remdesivir 10-d course may result in a small reduction in time to clinical improvement vs. control (5, 15)
Proportion receiving ventilation or ECMO at follow-up	Remdesivir 10-d course may result in a small reduction vs. control	Results from 1 subtrial vs. SC (15)	Remdesivir 10-d course probably results in a small reduction vs. control (4, 5, 7, 15)
Proportion with new need for ventilation or ECMO	Remdesivir 10-d course probably results in little to no difference vs. control	1 new RCT vs. SC (16)	Updated results confirm remdesivir 10-d course probably results in little to no difference vs. control (8, 16)
Serious adverse events	Remdesivir 10-d course probably results in a moderate reduction vs. control	1 new RCT (16) and results from 2 subtrials (14, 15), all vs. SC	Remdesivir 10-d course may result in a small reduction vs. control (4, 5, 7, 14, 15, 16)
Any adverse event	Remdesivir 10-d course may result in little to no difference vs. control	Results from 2 subtrials (14, 15) vs. SC	Remdesivir 10-d course may result in a small increase (4, 5, 7, 14, 15)
Remdesivir 10-d course vs. placebo; 2 RCTs, any severity COVID-19 (*n* = 1299 randomly assigned) (4, 5)			
Mortality	Remdesivir 10-d course may result in a small reduction vs. placebo (4, 5)	No new evidence	No change in conclusions
Proportion recovered*	Remdesivir 10-d course probably results in a moderate increase vs. placebo (4, 5)	No new evidence	No change in conclusions
Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase vs. placebo (5)	No new evidence	No change in conclusions
Hospital length of stay	Remdesivir 10-day course may result in a moderate reduction vs. placebo (4, 5)	No new evidence	No change in conclusions
Time to recovery	Remdesivir 10-day course may result in a large reduction vs. placebo (4) *Subgroup analyses (prespecified):* Time to recovery did not vary by age, sex, symptom duration (≤10 vs. >10 d), or disease severity (mild/moderate or severe)	No new evidence	No change in conclusions
Time to clinical improvement	Remdesivir 10-d course may result in a small reduction vs. placebo (5)	No new evidence	No change in conclusions
Proportion receiving invasive ventilation or ECMO at follow-up	Remdesivir 10-d course may result in a moderate reduction vs. placebo (4, 5)	No new evidence	No change in conclusions
Serious adverse events	Remdesivir 10-d course probably results in a moderate reduction vs. placebo (4, 5)	No new evidence	No change in conclusions
Any adverse event	Remdesivir 10-d course may result in a small reduction vs. placebo (4,5)	No new evidence	No change in conclusions

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Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
Remdesivir 10-d course vs. SC, any severity COVID-19; 3 RCTs and 2 subtrials (*n* = 6473 unique patients randomly assigned) (7, 8, 14, 15, 16)			
Mortality	Remdesivir 10-d course probably results in little to no difference vs. SC	–	Updated results confirm remdesivir 10-d course probably results in little to no difference vs. SC (7, 8, 16)
Proportion recovered*	Remdesivir 10-d course may result in a moderate increase in percentage recovered vs. SC	Results from 1 subtrial (15)	Updated results confirm remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. SC (7, 15)
Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase in percentage clinically improved vs. SC (7)	No new evidence	No change in conclusions
Hospital length of stay	No evidence	1 new RCT (16) and results from 1 subtrial (15)	Insufficient COE (15, 16)
Percentage hospitalized	The percentage of patients hospitalized between days 7 and 14 did not differ between the remdesivir 10-d course and SC groups (7, 8)	No new evidence	No change in conclusions
Time to recovery	Insufficient COE (7)	No new evidence	–
Time to clinical improvement	No evidence	Results from 1 subtrial (15)	Insufficient COE (15)
Proportion receiving ventilation or ECMO at follow-up	Remdesivir 10-d course may result in a small reduction vs. SC	Results from 1 sub-trial (15)	Updated results confirm remdesivir 10-d course may result in a small reduction vs. SC (7, 15)
Proportion with new need for ventilation	Remdesivir 10-d course probably results in little to no difference vs. SC	1 new RCT (16)	Updated results confirm remdesivir 10-d course probably results in little to no difference vs. SC (8, 16)
Serious adverse events	Remdesivir 10-d course may result in a small reduction vs. SC	1 new RCT (16) and results from 2 subtrials (14, 15)	Remdesivir 10-d course may result in little to no difference vs. SC (7, 14, 15, 16)
Any adverse event	Remdesivir 10-d course may result in a moderate increase vs. SC (7)	Results from 2 subtrials (14, 15)	Remdesivir 10-d course may result in a moderate increase vs. SC (7, 14, 15)
Remdesivir 5-d course vs. SC; 2 trials (*n* = 481 randomly assigned), moderate (7) and severe COVID-19 (12)			
Mortality	Remdesivir 5-d course may result in a small reduction vs. SC (7, 12)	No new evidence	No change in conclusions
Proportion recovered*	Remdesivir 5-d course may result in a moderate increase vs. SC (7)	No new evidence	No change in conclusions
Proportion with clinical improvement†	Remdesivir 5-d course may result in a moderate increase vs. SC (7)	No new evidence	No change in conclusions
Hospital length of stay	The percentage of persons hospitalized at days 11 and 14 did not differ between the remdesivir 5-d course and SC groups (7)	No new evidence	No change in conclusions
Time to recovery	Remdesivir 5-d course may result in a small reduction vs. SC (7, 12)	No new evidence	No change in conclusions
Time to clinical improvement	NR	–	–
Proportion receiving invasive ventilation or ECMO at follow-up	Remdesivir 5-d course may result in a small reduction vs. SC (7)	No new evidence	No change in conclusions
Proportion with new need for ventilation	Insufficient COE, based on 1 RCT (12) assessed as high risk of bias	No new evidence	No change in conclusions
Serious adverse events	Remdesivir 5-d course may result in a small reduction vs. SC (7)	No new evidence	No change in conclusions
Any adverse event	Remdesivir 5-d course may result in a small increase vs. SC (7)	No new evidence	No change in conclusions
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 798 randomly assigned), moderate (7) and severe (6) COVID-19 (excludes critical COVID-19)			
Mortality	Remdesivir 5-d course may result in a small reduction vs. 10-d course (6, 7)	No new evidence	No change in conclusions
Proportion recovered*	Remdesivir 5-d course may result in a moderate increase vs. 10-d course (6, 7)	No new evidence	No change in conclusions
Proportion with clinical improvement†	Remdesivir 5-d course may result in a moderate increase vs. 10-d course (6, 7)	No new evidence	No change in conclusions

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Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
Hospital length of stay	The percentage of persons hospitalized at days 11 and 14 did not differ between the remdesivir 5-d and 10-d course groups (7)	No new evidence	No change in conclusions
Time to recovery	Remdesivir 5-d course may result in a small reduction vs. 10-d course (6, 7)	No new evidence	No change in conclusions
Time to clinical improvement	NR	–	–
Proportion receiving invasive ventilation/ ECMO at follow-up	Remdesivir 5-d course may result in a small reduction vs. 10-d course (6, 7)	No new evidence	No change in conclusions
Serious adverse events	Remdesivir 5-d course may result in a moderate reduction vs. 10-d course (6, 7)	No new evidence	No change in conclusions
Any adverse event	Remdesivir 5-d course may result in a moderate reduction vs. 10-d course (6, 7)	No new evidence	No change in conclusions

COE = certainty of evidence; ECMO = extracorporeal membrane oxygenation; NR = not reported; RCT = randomized controlled trial; SC = standard of care.
* Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only (4), or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (5, 7), or achieving category 1 or 2 on the 7-point ordinal scale (category 1 = not hospitalized, no limitations on activities; category 2 = not hospitalized, limitations on activities) (15).
† Clinical improvement was defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital, whichever came first (5), or as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (6, 7).

Time to Clinical Improvement

Updated analyses, including new results from DisCoVeRy (15), confirm that remdesivir, compared with control, may result in a small reduction in median time to clinical improvement (clinical improvement was defined as days to improvement of 2 categories of the 7-point ordinal scale, ranging from 1 = not hospitalized and no limitations on activities to 7 = death) or hospital discharge up to day 29 (low COE) (5, 15).

Need for Ventilation or ECMO

Proportion Receiving Ventilation or ECMO at Follow-up

Our updated analyses, including new results from DisCoVeRy (15), show that remdesivir, compared with control, probably results in a small reduction in the proportion of patients receiving ventilation or ECMO at specific time points between days 11 and 15 (ARD, −4.5% [CI, −7.2% to −1.7%]) (moderate COE) (**Figure 2**, *B*) (4, 5, 7, 15).

New Need for Ventilation or ECMO

The inclusion of results from Abd-Elsalam and colleagues' study (16) with Solidarity confirms our prior conclusion that remdesivir, compared with control, probably results in little to no difference in new need for ventilation or ECMO within 28 days or 6 months (range of ARDs, 0.4% to 3.0%; 2 RCTs) (moderate COE) (**Figure 2**, *B*) (8, 16). On the basis of a sensitivity analysis, which included information from DisCoVeRy patients not previously included in the published Solidarity report, we concluded (due to inconsistency between RCT results) that remdesivir, compared with control, may result in little to no difference in new need for ventilation between 28 days to 6 months (3 RCTs) (8, 15, 16).

Adverse Events

Updated meta-analyses, including results from additional RCTs (14–16), show that remdesivir, compared with control, may lead to a small reduction in serious adverse events (ARD, −2.1% [CI, −6.5% to 2.2%]) (low COE) (**Figure 2**, *C*) (4, 5, 7, 14–16). Our last update found that remdesivir versus control probably results in a moderate reduction in serious adverse events (9). There was variation in how the trials reported serious adverse events, often including a combination of direct remdesivir toxicity and clinical findings consistent with COVID-19 progression (such as respiratory failure and need for endotracheal intubation). Updated meta-analyses, including results from 2 new RCTs (14, 15), show that remdesivir, compared with control, may result in a small increase in any adverse event (ARD, 4.9% [CI, −7.3% to 17.1%]; 5 RCTs) (low COE) (4, 5, 7, 14, 15).

Viral Clearance

Three RCTs assessed the effect of remdesivir on SARS-CoV-2 kinetics in the respiratory tract (5, 14, 15)–an intermediate outcome not assessed for COE (**Supplement Table 6**). All studies measured SARS-CoV-2 viral loads sequentially for 14 to 28 days after randomization using a quantitative, real-time, reverse transcriptase polymerase chain reaction test. All 3 RCTs showed that regardless of specimen site or collection methods (upper or lower airways; nasopharyngeal or oropharyngeal swabs or expectorated sputum), there was no statistically significant difference in the kinetics of SARS-CoV-2 load with remdesivir compared with control. All 3 RCTs also showed that the effect of remdesivir on SARS-CoV-2 clearance did not vary by symptom duration (stratified as ≤10 or >10 days [5]; <7 or ≥7 days [14]; or ≤7 days, −14 days, or >14 days [15]) or by baseline oxygen requirements (15).

Duration of Remdesivir Therapy: 5 Versus 10 Days (2 Trials)

No new RCTs compared a 5-day with a 10-day course of remdesivir. Hence, our prior conclusions, based on 2 RCTs (6, 7), remain unchanged (9) (**Table** and **Appendix Table**).

Discussion

This final update of our living review updates some findings comparing the effect of a 10-day course of remdesivir with control (placebo or SC) (4, 5, 7, 8, 14–16). The newly included RCTs strengthen previous findings on the benefit of remdesivir on the proportion of patients receiving ventilation or ECMO at follow-up but decreases the strength of previous findings on the reduction of serious adverse events with remdesivir. Another major change for this update was the low certainty of an increase in any adverse event with remdesivir (compared with a previous finding of little or no change in any adverse event). Other findings of the effect of a 10-day course of remdesivir (intervention) compared with either placebo or SC (control) are confirmed or unchanged.

Despite the reported strong antiviral effect of remdesivir against SARS-CoV-2 in preclinical models (22), 3 RCTs consistently show that remdesivir does not accelerate viral clearance in upper or lower airways compared with control, regardless of symptom duration. Another study published after our search date reported similar findings among outpatients with COVID-19 with symptoms for 7 days or less (23). These results suggest that remdesivir's effectiveness is not related to viral load clearance and that using SARS-CoV-2 clearance in upper and lower airways is not a valid surrogate for clinical outcomes (24).

Cost-effectiveness models assume that remdesivir shortens duration of hospitalization for patients with COVID-19 (25). Contrary to this assumption, 1 large propensity-matched retrospective cohort study among veterans hospitalized at VA medical centers ($n = 2344$) found that remdesivir treatment was associated with prolonged hospitalization without improved survival (26). The clustering of discharges suggested that patients ready for medical discharge were hospitalized solely to complete the prescribed course of remdesivir—a practice inconsistent with RCT protocols and treatment guidelines (4, 27, 28).

Given that this is our last living review update, we note ongoing trials of remdesivir for COVID-19 evaluating formulations and populations not previously studied, which may alter practice and policy. These include inhaled and oral formulations of remdesivir and studies including previously excluded populations (pregnant women, children, and patients with renal dysfunction) (29). In addition, 1 placebo-controlled RCT was published after our last search date, which is the only study done among outpatient adults and assessing the effect on hospitalizations. The study evaluated remdesivir given intravenously daily for 3 days to high-risk, unvaccinated outpatients with COVID-19 with 7 days or less of symptoms (23). Compared with placebo, remdesivir reduced COVID-19–related hospitalization at day 28 (0.7% [2 of 279] vs. 5.3% [15 of 283]; $P = 0.008$). There were no deaths in either group. The study enrolled patients before the emergence of the Delta or Omicron variants of SARS-CoV-2 as the dominant strain and was terminated early due to "the changing epidemiology and adoption of additional treatment options at the time" (23, 30).

In conclusion, in hospitalized adults with COVID-19, remdesivir probably results in little to no difference in mortality. However, remdesivir probably increases the proportion of patients recovered and may reduce time to clinical improvement and length of hospitalization. Remdesivir may lead to a small reduction in serious adverse events but may lead to a small increase in any adverse event. Compared with a 5-day course of remdesivir, a 10-day course may have little to no benefit and has higher drug cost among patients not requiring mechanical ventilation or ECMO.

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Acknowledgment: The authors thank the DisCoVeRy study authors Florence Ader, Maya Hites, Drifa Belhadi, Alpha Diallo, Hèlene Esperou, Charles Burdet, and France Mentré for providing unpublished data for patients unique to DisCoVeRy who were not included in the WHO Solidarity report.

Financial Support: The original review was funded by the VA, Office of Research and Development, Health Services Research and Development Service, Evidence Synthesis Program.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-4784.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Mr. MacDonald (e-mail, Roderick.macdonald@va.gov). *Data set:* See the **Supplement** (available at Annals.org).

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Appendix Table. Effect of Remdesivir in Randomized Controlled Studies

Comparison	Study, Year (Reference); Assessment Time Point; Disease Severity Based on O_2 Status at Admission	Absolute Effect of Remdesivir vs. Control	Certainty of Evidence*	Summary†
All-cause mortality				
Remdesivir 10-d course vs. placebo or SC; 5 trials (*n* = 7342)	Beigel et al (ACTT-1), 2020 (4); Wang et al, 2020 (5); Spinner et al (SIMPLE-2), 2020 (7); Solidarity 2021 (8); Abd-Elsalam et al 2021 (16); 11 d to 6 mo Any severity–no O_2 at baseline 25%; receiving O_2 or ventilation (noninvasive and invasive) at baseline 75%	10.5% (393/3735) vs. 11.1% (401/3607) Pooled ARD, −0.7% (95% CI, −2.4% to 1.0)	Moderate‡	Remdesivir 10-d course probably results in little to no difference in mortality vs. placebo or SC
Remdesivir 10-d course vs. placebo; 2 trials (*n* = 1298)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13% Wang et al, 2020 (5); 28 d Severe–no O_2 1%	10.9% (59/541) vs.14.8% (77/521) ARD, −3.9% (CI, −7.9% to 0.1%) 13.9% (22/158) vs. 12.8% (10/78) ARD, 1.1% (−8.1% to 10.3%)	Low§	Remdesivir 10-d course may result in a small reduction in mortality vs. placebo Range of ARDs, −3.9% to 1.1%
Remdesivir 10-d course vs. SC; 3 trials (*n* = 5844)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 84% Solidarity, 2021 (8); 28 d (*reported only during initial hospitalization; follow-up ceased after discharge*) Severe–no O_2 24% Abd-Elsalam et al, 2021 (16) O_2 at baseline NR. Noted as "mild to moderate symptoms."	1.0% (2/193) vs. 2.0% (4/200) ARD, −1.0% (CI, −3.4% to 1.4%) 11.0% (301/2743) vs. 11.2% (303/2708) ARD, −0.2% (CI, −1.9% to 1.5%) 9.0% (9/100) vs. 7.0% (7/100) ARD, 2% (CI, −5.5% to 9.5%)	Moderate‡	Remdesivir 10-d course probably results in little to no difference in mortality vs. standard care 10.3% (312/3036) vs. 10.4% (314/3008) Pooled ARD, −0.4% (CI, −1.7% to 1.0%)
Remdesivir 5-d course vs. SC; 2 trials (*n* = 461)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 82% Mahajan et al, 2021 (12); 24 d Severe–no O_2 0%	0% (0/191) vs. 2.0% (4/200) ARD, −2.0% (CI, −4.2% to 0.2%) Per protocol (days 12 to 24) 14.7% (5/34) vs. 8.3% (3/36) ARD, 6.4% (CI, −8.6% to 21.3%)	Low‖	Remdesivir 5-d course may result in a small reduction in mortality vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe–no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 86%	8.0% (16/200) vs. 10.7% (21/197) ARD, −2.7% (CI, −8.4% to 3.1%) 0% (0/191) vs. 1.0% (2/193) ARD, −1.0% (CI, −2.8% to 0.7%)	Low¶	Remdesivir 5-d course may result in a small reduction in mortality vs. 10-d course Range of ARDs, −2.7% to −1.0%
Proportion of patients recovered, defined as discharge from the hospital or hospitalization for infection control purposes only (4) or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (5-7) or discharge from the hospital, with or without limitations on activities (15)				
Remdesivir 10-d course vs. placebo or SC; 4 trials (*n* = 2514)	Beigel et al (ACTT-1), 2020 (4); Wang et al, 2020 (5); Spinner et al (SIMPLE-2), 2020 (7); Ader et al (DisCoVeRy), 2021 (15); 28 to 29 d Any severity–no O_2 24%; any O_2/ventilation 76%	73.0% (948/1298) vs. 66.8% (812/1216) Pooled ARD, 6.5% (CI, 3.0% to 10.0%)	Moderate‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. placebo or SC
Remdesivir 10-d course vs. placebo; 2 trials (*n* = 1289)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13% Wang et al, 2020 (5); 28 d Severe–no O_2 1%	73.8% (399/541) vs. 67.6% (352/521) ARD, 6.2% (CI, 0.7% to 11.7%) 70.7% (106/150) vs. 63.6% (49/77) ARD, 7.0% (CI, −6.0% to 20.0%)	Moderate‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. placebo Range of ARDs, 6.2% to 7.0%
Remdesivir 10-d course vs. SC; 2 trials (*n* = 1225)	Spinner et al (SIMPLE-2), 2020 (7); 28 d Moderate–no O_2 84% Ader et al (DisCoVeRy), 2021 (15): 29 d Severe–no O_2 1%	92.2% (178/193) vs. 85% (170/200) ARD, 7.2% (CI, 1.0% to 13.5%) 64% (265/414) vs. 57.7% (241/418) ARD, 6.4% (CI, −0.3% to 13.0%)	Moderate‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs. SC Range of ARDs, 6.4% to 7.2%
Remdesivir 5-d course vs. SC; 1 trial (*n* = 391)	Spinner et al (SIMPLE-2), 2020 (7); 28 d Moderate–no O_2 82%	91.6% (175/191) vs. 85% (170/200) ARD, 6.6% (CI, 0.3% to 12.9%)	Low§	Remdesivir 5-d course may result in a moderate increase in percentage recovered vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe–no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 86%	64.5% (129/200) vs. 53.8% (106/197) Baseline-adjusted ARD, 6.3% (CI, −2.8% to 15.4%) 73.8% (141/191) vs. 68.4% (132/193) ARD, 5.4% (CI, −3.6% to 14.5%)	Low¶	Remdesivir 5-d course may result in a moderate increase in percentage recovered vs. 10-d course Range of ARDs, 5.4% to 6.3%
Proportion with clinical improvement, defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death), or live discharge from the hospital, whichever came first (5) as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) (6, 7)				
Remdesivir 10-d course vs. placebo (5) or SC (7); 2 trials (*n* = 629)	Wang et al, 2020 (5); 28 d Severe–no O_2 1% Spinner et al (SIMPLE-2), 2020 (7); 28 d Moderate–no O_2 84%	65.2% (103/158) vs. 57.7% (45/78) ARD, 7.5% (CI, −5.7% to 20.7%) 90.2% (174/193) vs. 83% (166/200) ARD, 7.2% (CI, 0.5% to 13.8%)	Low§	Remdesivir 10-d course may result in a moderate increase in percentage with clinical improvement vs. placebo or SC Range of ARDs, 7.2% to 7.5%

Continued on following page

Appendix Table–Continued

Comparison	Study, Year (Reference); Assessment Time Point; Disease Severity Based on O_2 Status at Admission	Absolute Effect of Remdesivir vs. Control	Certainty of Evidence*	Summary†
Remdesivir 5-d course vs. SC; 1 trial (*n* = 391)	Spinner et al (SIMPLE-2), 2020 (7); 28 d Moderate–no O_2 82%	89.5% (171/191) vs. 83% (166/200) ARD, 6.5% (CI, −0.3% to 13.3%)	Low§	Remdesivir 5-d course may result in a moderate increase in percentage with clinical improvement vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe—no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate—no O_2 86%	64.5% (129/200) vs. 54.3% (107/197) Baseline-adjusted ARD, 6.5% (CI, −2.8% to 15.7%) 70.2% (134/191) vs. 65.3% (126/193) ARD, 4.9% (CI, −4.5% to 14.2%)	Low¶	Remdesivir 5-d course may result in a moderate increase in percentage with clinical improvement vs. 10-d course Range of ARDs, 4.9% to 6.5%
Hospital LOS				
Remdesivir 10-d course vs. control; 4 trials (*n* = 2331)	Beigel et al, (ACTT-1), 2020 (4); Wang et al, 2020 (5); Ader et al (DisCoVeRy), 2021 (15); Abd-Elsalam et al, 2021 (16) *See individual study results below*	Outcome not pooled, difference in medians ranged from 6 to −2 d shorter in LOS	Low**	Remdesivir 10-d may result in up to a moderate reduction in LOS vs. placebo or SC
Remdesivir 10-d course vs. placebo; 2 trials (*n* = 1299)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13% Wang et al, 2020 (5); 28 d Severe–no O_2 1%	*Initial hospitalization* Median, 12 d (IQR, 6 to 28 d) vs. 17 d (IQR, 8 to 28 d) MD, −5 d (CI, −7.7 to −2.3 d) Median, 25 d (IQR, 16 to 38 d) vs. 24 d (IQR, 18 to 36 d) MD, 0 d (CI, −4.0 to 4.0 d)	Low††	Remdesivir 10-d course may result in a moderate reduction in LOS vs. placebo
Remdesivir 10-d course vs. SC; 2 trials (*n* = 1032)	Ader et al (DisCoVeRy), 2021 (15); 29 d Severe–no O_2 1% Abd-Elsalam et al, 2021 (16); 6 mo O_2 at baseline NR. Noted as "mild to moderate symptoms."	Median, 15 d (IQR, 10 to 29 d) vs. 13 d (IQR, 8 to 29 d) HR, 0.94 (CI, 0.80 to 1.11) Median, 10 d (IQR, 8 to 13.8 d) vs. 16 d (IQR, 12 to 21 d)	Insufficient‡‡	
Percentage hospitalized				
Remdesivir 10-d course vs. SC	Solidarity, 2021 (8), severe–no O_2 24%: no differences in percentage hospitalized at 7 (69% vs. 59%) and 14 d (22% vs. 19%) Spinner et al (SIMPLE-2), 2020 (7), moderate–no O_2 84%: no differences in percentage hospitalized at 11 (34% vs. 38%) and 14 d (23% vs. 31%)			
Remdesivir 5-d course vs. SC	Spinner et al (SIMPLE-2), 2020 (7), moderate–no O_2 82%: no differences in percentage hospitalized at 11 (30% vs. 38%) and 14 d (23% vs. 31%)			
Remdesivir 5-d course vs. remdesivir 10-d course	Spinner et al (SIMPLE-2), 2020 (7), moderate–no O_2 86%: no differences in percentage hospitalized at 11 (30% vs. 34%) and 14 d (23% vs. 23%)			
Time to recovery				
Remdesivir 10-d course vs. placebo or SC; 2 trials (*n* = 2506)	Beigel et al, (ACTTT-1), 2020 (4); Spinner et al (SIMPLE-2), 2020 (7) 11 to 29 d Any severity–no O_2 38%; any O_2/ventilation 62%	Difference in medians ranged from 5 to −1 d shorter in time to recovery	Low**	Remdesivir 10-d course may result in an uncertain reduction in time to recovery in patients with moderate severity at day 11 and a large reduction in patients with severe disease at day 29 vs. placebo or SC
Remdesivir 10-d course vs. placebo; 1 trial (*n* = 1062)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13%	Median, 10 d (CI, 9 to 11 d) vs. 15 d (CI, 13 to 18 d); $P < 0.001$ Rate ratio, 1.29 (CI, 1.12 to 1.49)	Low**	Remdesivir 10-d course may result in large reduction in time to recovery vs. placebo *(Time to recovery did not vary by age, sex, symptom duration (≤10 vs. >10 d) or disease severity)* (1)
Remdesivir 10-d course vs. SC; 1 trial (*n* = 393)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 84%	Median, 8 d (IQR, 4 to 13 d) vs. 7 d (IQR, 4 to 15 d); HR, 1.11 (CI, 0.90 to 1.37)	Insufficient‡‡	
Remdesivir 5-d course vs. SC; 2 trials (*n* = 461)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 82% Mahajan et al, 2021 (12); day 10 through day 20 Severe–no O_2 0%	Median, 6 d (IQR, 5 to 10 d) vs. 7 d (IQR, 4 to 15 d); HR, 1.18 (CI, 0.96 to 1.45) Data NR. Trialists noted patients in both groups "had an equal time to recovery (not defined) between 10 and 20 days."	Low‖	Remdesivir 5-d course may result in a small reduction in time to recovery vs. SC

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Appendix Table–Continued

Comparison	Study, Year (Reference); Assessment Time Point; Disease Severity Based on O_2 Status at Admission	Absolute Effect of Remdesivir vs. Control	Certainty of Evidence*	Summary†
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (n = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe–no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 86%	Median, 10 d (IQR, 6 to 18 d) vs. 11 d (IQR, 7 to not able to estimate); P value NS; HR, 0.81 (CI, 0.64 to 1.04) Median, 6 d (IQR, 5 to 10 d) vs. 8 d (IQR, 4 to 13 d); HR, NR	Low¶	Remdesivir 5-d course may result in a small reduction in time to recovery vs. a 10-d course
Time to clinical improvement				
Remdesivir 10-d course vs. placebo or SC; 2 trials (n = 1069)	Wang et al, 2020 (5); Ader et al (DisCoVeRy), 2021 (15) 11 to 29 d Severe–no O_2 1%	Difference in medians ranged from 2 to −1 d shorter in time to clinical improvement	Low**	Remdesivir 10-d course may result in a small reduction in time to clinical improvement vs. placebo or SC
Remdesivir 10-d course vs. placebo; 1 trial (n = 237)	Wang et al, 2020 (5); 28 d Severe–no O_2 1%	Median, 21 d (IQR, 13 to 28 d) vs. 23 d (IQR, 18 to 36 d); HR, 1.23 (CI, 0.87 to 1.75)	Low§	Remdesivir 10-d course may result in a small reduction in time to clinical improvement vs. placebo
Remdesivir 10-d course vs. SC; 1 trial (n = 832)	Ader et al (DisCoVeRy), 2021 (15); 29 d Severe–no O_2 1%	Median, 12 d (IQR, 8 to 24 d) vs. 11 d (IQR, 7 to 26 d); HR, 0.92 (CI, 0.79 to 1.08)	Insufficient‡‡	Remdesivir 10-d course may result in an uncertain effect on time to clinical improvement vs. SC
Proportion receiving invasive ventilation or ECMO at follow-up (Spinner et al [SIMPLE-2] on day 11, Wang et al on day 14, and Beigel et al [ACTT-1] and Ader et al [DisCoVeRy] on day 15)				
Remdesivir 10-d course vs. placebo or SC; 4 trials (n = 2518)	Beigel et al (ACTT-1), 2020 (4); Wang et al, 2020 (5); Spinner et al (SIMPLE-2) 2020 (7); Ader et al (DisCoVeRy), 2021 (15) 11 to 15 d Any severity–no O_2 24%; any O_2/ventilation 76%	12.5% (162/1301) vs. 17.3% (211/1217) Pooled ARD, −4.5% (CI, −7.2% to −1.7%)	Moderate‡	Remdesivir 10-d course probably results in a small reduction in proportion on invasive ventilation or ECMO at follow-up vs. placebo or SC
Remdesivir 10-d course vs. placebo; 2 trials (n = 1299)	Beigel et al (ACTT-1), 2020 (4) Severe–no O_2 13% Wang et al, 2020 (5) Severe–no O_2 1%	17.6% (95/541) vs. 23.2% (121/521) ARD, −5.7% (CI, −10.5% to −0.8%) 2.6% (4/153) vs. 9.0% (7/78) ARD, −6.4% (CI, −13.2% to 0.5%)	Low§	Remdesivir 10-d course may result in a moderate reduction in proportion receiving invasive ventilation or ECMO at follow-up vs. placebo Range of ARDs, −5.7% to −6.4%
Remdesivir 10-d course vs. SC; 2 trials (n = 1225)	Spinner et al (SIMPLE-2), 2020 (7) Moderate–no O_2 84% Ader et al (DisCoVeRy), 2021 (15); 29 d Severe–no O_2 1%	0.5% (1/193) vs. 2.0% (4/200) ARD, −1.5% (CI, −3.7% to 0.7%) 15.0 % (62/414) vs. 18.9% (79/418) ARD, −3.9% (CI, −9.0% to 1.2%)	Low§	Remdesivir 10-d course may result in a small reduction in proportion receiving invasive ventilation or ECMO at follow-up vs. SC Range of ARDs, −3.9% to −1.5%
Remdesivir 5-d course vs. SC; 1 trial (n = 391)	Spinner et al (SIMPLE-2), 2020 (7) Moderate–no O_2 82%	0% (0/191) vs. 2.0% (4/200) ARD, −2.0% (CI, −4.2% to 0.2%)	Low§	Remdesivir 5-d course may result in a small reduction in proportion receiving invasive ventilation or ECMO at follow-up vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (n = 781)	Goldman et al (SIMPLE-1), 2020 (6) Severe–no O_2 14% Spinner et al (SIMPLE-2), 2020 (7) Moderate–no O_2 86%	8.0% (16/200) vs. 16.8% (33/197) ARD, −8.8% (CI, −15.2% to −2.3%) 0% (0/191) vs. 0.5% (1/193) ARD, −0.5% (CI, −1.9% to 0.9%)	Low¶	Remdesivir 5-d course may result in a small reduction in proportion receiving invasive ventilation or ECMO vs. 10-d course at follow-up Range of ARDs, −8.8% to −0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial; i.e., severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
New need for ventilation (invasive or noninvasive ventilation or ECMO) within 28 d or 6 mo				
Remdesivir 10-d course vs. SC; 2 trials (n = 5164)	Solidarity, 2020 (8); 28 d Severe–no O_2 24% Abd-Elsalam et al, 2021 (16); 6 mo O_2 at baseline NR. Noted as "mild to moderate symptoms."	11.9% (295/2489) vs. 11.5% (284/2475) ARD, 0.4% (CI, −1.4% to 2.2%) 11.0% (11/100) vs. 8.0% (8/100) ARD, 3.0% (CI, −5.1% to 11.1%)	Moderate‡	Remdesivir 10-d course probably results in little to no difference in new need for ventilation vs. SC Range of ARDs, 0.4% to 3.0%
Remdesivir 5-d course vs. SC; 1 trial (n = 70)	Mahajan et al, 2021 (12) Day 12 through day 24 Severe–no O_2 0%	11.8% (4/34) vs. 5.6% (2/36) ARD, 6.2% (CI, −7.0% to 19.4%)	Insufficient§§	

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Appendix Table–Continued

Comparison	Study, Year (Reference); Assessment Time Point; Disease Severity Based on O_2 Status at Admission	Absolute Effect of Remdesivir vs. Control	Certainty of Evidence*	Summary†
Serious adverse events (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-d course vs. placebo or SC; 6 trials (*n* = 2627)	Beigel et al (ACTT-1), 2020 (4); Wang et al, 2020 (5); Spinner et al (SIMPLE 2), 2020 (7); Barratt-Due et al (NOR-Solidarity), 2021 (14); Ader et al (DisCoVeRy), 2021 (15); Abd-Elsalam et al, 2021 (16) 11 to 29 d Any severity–no O_2 24%; any O_2/ventilation 76%	21.8% (312/1428) vs. 24.6% (344/1499) Pooled ARD, −2.1% (CI, −6.5% to 2.2%)	Low††	Remdesivir 10-d course may result in a small reduction in serious adverse events vs. control
Remdesivir 10-d course vs. placebo; 2 trials (*n* = 1299)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13% Wang et al, 2020 (5); 28 d Severe–no O_2 1%	24.6% (131/532) vs. 31.6% (163/516) ARD, −7.0% (CI, −12.4% to 1.5%) 18.1% (28/155) vs. 25.6% (20/78) ARD, −7.6% (CI, −19.0% to 3.9%)	Moderate‡	Remdesivir 10-d course probably results in a moderate reduction in serious adverse events vs. placebo Range of ARDs, −7.6% to −7.0%
Remdesivir 10-d course vs. SC; 4 trials (*n* = 1546)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 84% Ader et al (DisCoVeRy), 2021 (15); 29 d Severe–no O_2 1% Barratt-Due et al (NOR-Solidarity), 2021 (14): 90 d O_2 at baseline NR (overall, Solidarity severe) Abd-Elsalam et al, 2021 (16): 6 mo O_2 at baseline NR. Noted as "mild to moderate symptoms."	5.2% (10/193) vs. 9.0% (18/200) ARD, −3.8% (CI, −8.9% to 1.2%) 33.3% (135/406) vs. % 31.1% (130/418) ARD, 2.2% (CI, −4.2% to 8.5%) 19.0% (8/42) vs. 14.9% (13/87) ARD, 4.1% (CI, −9.9% to 18.1%) 0% (0/100) vs. 0% (0/100) ARD, 0% (CI, −1.9% to 1.9%)	Low††	Remdesivir 10-d course may result in in little to no difference in serious adverse events vs. SC 20.6% (153/741) vs. 20.0% (161/805) Pooled ARD, −0.2% (CI, −1.95% to 1.5%)
Remdesivir 5-d course vs. SC; 1 trial (*n* = 391)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 82%	4.7% (9/191) vs. 9.0% (18/200) ARD, −4.3% (CI, −9.3% to 0.7%)	Low§	Remdesivir 5-d course may result in a small reduction in serious adverse events vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe–no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 86%	21.0% (42/200) vs. 34.5% (68/197) ARD, −13.5% (CI, −22.2% to −4.8%) 4.7% (9/191) vs. 5.2% (10/193) ARD, −0.5% (CI, −4.8% to 3.9%)	Low††	Remdesivir 5-d course may result in a moderate reduction in serious adverse events vs. 10-d course Range of ARDs, 13.5% to 0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial; i.e., severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
Any adverse event (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-d course vs. placebo or SC; 5 trials (*n* = 2627)	Beigel et al (ACTT-1), 2020 (4); Wang et al, 2020 (5); Spinner et al (SIMPLE 2), 2020 (7); Barratt-Due et al (NOR-Solidarity), 2021 (14); Ader et al (DisCoVeRy), 2021 (15) 11 to 29 d Any severity–no O_2 24%; any O_2/ventilation 76%	58.8% (781/1328) vs. 55.7% (724/1299) Pooled ARD, 4.9% (CI, −7.3% to 17.1%)	Low††	Remdesivir 10-d course may result in a small increase in any adverse events vs. control
Remdesivir 10-d course vs. placebo; 2 trials (*n* = 1281)	Beigel et al (ACTT-1), 2020 (4); 29 d Severe–no O_2 13% Wang et al, 2020 (5); 28 d Severe–no O_2 1%	57.3% (305/532) vs. 62.6% (323/516) ARD, −5.3% (CI, −11.2% to 0.7%) 65.8% (102/155) vs. 64.1% (50/78) ARD, 1.7 (CI, −11.3% to 14.7%)	Low§	Remdesivir 10-d course may result in a small reduction in any adverse events vs. placebo Range of ARDs, −5.3% to 1.7%
Remdesivir 10-d course vs. SC; 3 trials (*n* = 393)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate–no O_2 84% Ader et al (DisCoVeRy), 2021 (15): 29 d Severe–no O_2 1% Barratt-Due et al (NOR-Solidarity), 2021 (14): 90 d O_2 at baseline NR (overall, Solidarity severe)	58.5% (113/193) vs. 47% (93/200) ARD, 12.0% (CI, 2.2% to 21.9%) 59.4% (241/406) vs. 56.5% (236/418) ARD, 2.9% (CI, −3.8% to 9.6%) 47.6% (20/42) vs. 25.3% (22/87) ARD, 22.3% (CI, 4.7% to 40.0%)	Low††	Remdesivir 10-d course may result in a moderate increase in any adverse events vs. SC 58.3% (374/641) vs. 49.8% (351/705) Pooled ARD, 7.3% (CI, 2.0% to 12.6%)

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Appendix Table–Continued

Comparison	Study, Year (Reference); Assessment Time Point; Disease Severity Based on O_2 Status at Admission	Absolute Effect of Remdesivir vs. Control	Certainty of Evidence*	Summary†
Remdesivir 5-d course vs. SC; 1 trial (*n* = 391)	Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate-no O_2 82%	51.3% (98/191) vs. 46.5% (93/200) ARD, 4.8% (CI, −5.1% to 14.7%)	Low§	Remdesivir 5-d course may result in a small increase in any adverse events vs. SC
Remdesivir 5-d course vs. remdesivir 10-d course; 2 trials (*n* = 781)	Goldman et al (SIMPLE-1), 2020 (6); 14 d Severe-no O_2 14% Spinner et al (SIMPLE-2), 2020 (7); 11 d Moderate-no O_2 86%	70.5% (141/200) vs. 73.6% (145/197) ARD, −3.1% (CI, −11.9% to 5.7%) 51.3% (98/191) vs. 58.5% (113/193) ARD, −7.2% (CI, −17.2% to 2.7%)	Low¶	Remdesivir 5-d course may result in a moderate reduction in any adverse events vs. 10-d course Range of ARDs, −7.2% to −3.1%

ACTT-1 = Adaptive COVID-19 Treatment Trial; ARD = absolute risk difference; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; IQR = interquartile range; LOS = length of stay; MD = mean difference; NR = not reported; NS = not statistically significant; O_2 = oxygen; SC = standard care; SIMPLE-1 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19); SIMPLE-2 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment.

* GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence are as follows: High certainty: We are very confident that the true effect lies close to the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate. The true effect is probably close to the estimate of the effect, but a possibility exists 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 probably substantially different from the estimate of the effect.

† Thresholds for determining magnitude by outcome are as follows: *All-cause mortality:* little or no effect, <1%; small effect, 1%–2.9%; moderate effect, 3%–4.9%; large effect, ≥5%. *Recovery:* little or no effect, <2%; small effect, 2%–4.9%; moderate effect, 5%–9.9%; large effect, ≥10%. *Clinical improvement:* little or no effect, <2%; small effect, 2%–4.9%; moderate effect, 5%–9.9%; large effect, ≥10%. *LOS:* little or no effect, <1 d; small effect, ≥1–2 d; moderate effect, >2 to <3 d; large effect, ≥3 d. *Time to recovery or clinical improvement:* little or no effect, <1 d; small effect, ≥1–2 d; moderate effect, >2 to <3 d; large effect, ≥3 d. *Ventilation or ECMO:* little or no effect, <1%; small effect, 1%–4.9%; moderate effect, 5%–9.9%; large effect, ≥10%. *Any adverse event:* little or no effect, <2%; small effect, 2%–4.9%; moderate effect, 5%–19.9%; large effect, ≥20%. *Severe adverse event:* little or no effect, <1%; small effect, 1%–4.9%; moderate effect, 5%–9.9%; large effect, ≥10%.

‡ Downgraded for imprecision.

§ Downgraded 2 levels for imprecision (very wide CIs) and/or sparse data.

‖ Downgraded 2 levels for imprecision (very wide CIs) and/or sparse data. The Mahajan trial (12) assessed as high risk of bias, did not affect the overall certainty of evidence or magnitude of effect.

¶ Downgraded 2 levels for study limitations and imprecision (wide CIs).

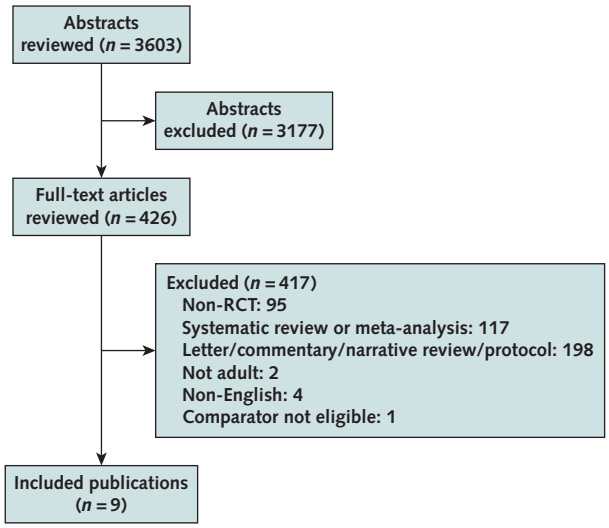
** Downgraded 2 levels for difficulty in interpreting precision.

†† Downgraded 2 levels for imprecision and inconsistency.

‡‡ Downgraded to insufficient for difficulty in interpreting results, imprecision (very wide CIs), and/or inconsistency.

§§ Downgraded to insufficient for study limitations and imprecision (very wide CIs).

Appendix Figure. Evidence search and selection.



RCT = randomized controlled trial.