COVID-19: Remdesivir for Adults – A Living Review

Updated February 2022

U.S. Department of Veterans Affairs
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WHAT'S NEW

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Search current as of October 19, 2021

This is our fifth and final update. It revises findings from our update of August 9, 2021 and includes a literature search through October 19, 2021. This update adds 1 small RCT and DisCoVeRy, which is an add-on sub-study of WHO Solidarity. The results did not change our prior conclusion that overall, in hospitalized adults with COVID-19, remdesivir probably results in little to no difference in mortality and probably 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. Effect on hospital length of stay or percent remaining hospitalized is mixed. The sub-study is consistent with 2 prior studies that found no difference in rate of viral clearance with remdesivir as compared to control.

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the **Minneapolis VA Health Care System, Minneapolis, MN**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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QUESTIONS

What are the effectiveness and harms of remdesivir for patients with COVID-19?

Do effectiveness and harms vary by symptom duration, disease severity, and treatment duration?

WHAT DID WE KNOW?

Our prior VA-ESP report of 6 randomized trials (RCTs) and 1 add-on sub-study of WHO Solidarity[1] concluded that in hospitalized adults with COVID-19, remdesivir probably results in little to no reduction in mortality, a moderate increase in percent recovered, and a moderate reduction in serious adverse events.[2] Effects on mortality may vary by initial respiratory support but not by other patient or disease factors. Effect on hospital length of stay or percent hospitalized is mixed (4 RCTs), in part due to continued hospitalization while administering remdesivir. For adults not receiving mechanical ventilation or extracorporeal membrane oxygenation, a 5-day course of remdesivir may provide benefits over, and fewer harms than, a 10-day course. Trials excluded pregnant women or those with severe hepatic or renal dysfunction. The FDA has approved remdesivir for patients over age 12 and weighing more than 40kg hospitalized with COVID-19, and recently expanded its use to certain non-hospitalized adults and pediatric patients for the treatment of mild-to-moderate disease in order to reduce the risk of hospitalization in high-risk patients.[3] The FDA has noted side effects of remdesivir.[4] Remdesivir is the only drug so far to receive federal approval for COVID-19.

WHAT IS NEW?

UPDATED: 02/02/2022

SEARCH CURRENT AS OF 10/19/2021

This update adds 1 small (N=209) RCT[5] and add-on sub-study DisCoVeRy (N=832)[6] in addition to our previously included 6 RCTs.[7-12] The newest RCT was an open-label randomized controlled trial conducted at 2 sites in Egypt (Supplemental Table 1).[5] The study compared a 10-day course of remdesivir (n=100) to standard care (SC) (n=100) for adults hospitalized with laboratory-confirmed COVID-19. The primary outcomes were the length of hospital stay and mortality. The need for ventilation was a secondary outcome. Median age was 54 years and 60% were male. The median duration of symptoms and stratification of patients by baseline oxygen requirements were not reported. However, the mean baseline oxygen saturation, reported as 88.5% (without a report on level of oxygen supplementation), was consistent with both NIH and WHO definitions of severe COVID-19.

DisCoVeRy, a sub-study trial of Solidarity, was an open-label, adaptive, multicenter RCT conducted in 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg) (Supplemental Table 1).[6] DisCoVeRy compared a 10-day course of remdesvir (n=414) to SC (n=418) for adults hospitalized with laboratory-confirmed COVID-19 with clinical hypoxia or need for oxygen supplementation (severe or critical disease; Supplemental Table 10), as an add-on trial to Solidarity; 53% (440/832) of DisCoVeRy participants had been previously included in Solidarity. The primary outcome for DisCoVeRy was clinical status at day 15 measured by the WHO 7-point ordinal scale, an outcome not reported by Solidarity. Additional new outcomes

reported were time to improvement, length of hospitalization, proportion needing ventilation on day 15, any adverse event, serious adverse events, and SARS-CoV-2 kinetics. Among all participants, median age was 64 years, 70% were male, and 69% were white. The median duration of symptoms was 9 days. At baseline, 77% were on supplemental oxygen, 4% on non-invasive ventilation, and 18% on invasive ventilation. 40% of all patients received corticosteroids. Our original conclusions, derived from the previously included 6 RCTs,[7-12] are unchanged for 2 primary outcomes — remdesivir probably results in little to no difference in mortality and probably results in a moderate increase in the proportion of patients recovered by day 29. 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 ECMO at specific follow-up times (4 RCTs). New RCTs also alter the conclusions for harms — remdesivir, as compared with control, may lead to a small reduction in serious adverse events but may lead to a small increase in any adverse event. Summary of conclusions and updated findings are detailed in Table 1.

WHAT DO WE CONCLUDE?

The results of the new RCT study and 1 new sub-trial did not change our prior conclusion that overall, a 10-day remdesivir course probably results in little to no reduction in mortality (5 RCTs). Remdesivir probably results in a small reduction in proportion on mechanical ventilation (4 RCTs) but probably results in little to no difference in new need for ventilation versus SC (2 RCTs). Remdesivir probably results in a moderate increase in percent recovered, may lead to a small decrease in serious adverse events, and may result in a large reduction in time to recovery. The new sub-trial is consistent with 2 prior studies that also found no difference in rate of viral clearance with remdesivir as compared to control (placebo or SC). Effect on hospital length of stay or percent remaining hospitalized is mixed. In contrast to the noted large reduction in time to recovery with remdesivir in RCTs, the large VA-wide retrospective study found that patients treated at VHA medical centers and receiving remdesivir had a significantly longer duration of hospitalization as compared to matched controls. Effects on mortality may vary by initial respiratory support but not by other patient or disease factors including symptom or hospitalization duration, age, sex, race/ethnicity, smoking status, comorbidities, geographic location, or corticosteroid use.

Remdesivir may increase mortality in those already on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Recovery effects may not vary by age, sex, symptom duration, or disease severity. Remdesivir probably reduces serious adverse effects that include measures of COVID-19 disease progression. Compared with 10 days, a 5-day remdesivir course may reduce mortality and need for mechanical ventilation, may increase recovery and/or clinical improvement by small to moderate amounts, and may reduce serious adverse events among patients not requiring mechanical ventilation at baseline. Drug costs would be lower. Pregnant women, children under age 12, and individuals with severe renal and hepatic dysfunction have been excluded from studies. Caution and monitoring are indicated if remdesivir is used in these individuals. The FDA notes that remdesivir side effects include elevated liver enzymes and allergic reactions (which may include changes in blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling (*eg*, lips, around eyes, under the skin), rash, nausea, sweating, or shivering).[4]

The FDA has approved the administration of remdesivir in a hospital or healthcare setting capable of providing acute care comparable to inpatient hospital care. Additionally, the FDA has recently expanded approval for treatment to certain high-risk adult and pediatric outpatients patients to reduce the risk of hospitalization.[3] Prior RCTs protocols and treatment guideline recommendations indicate that patients should not be hospitalized solely to complete a full 5- or 10-day treatment course of remdesivir. However, the VA study showed hospital discharges clustering around completion of a 5-day remdesivir course as well as a longer hospitalization duration in patients receiving remdesivir. These findings suggest that many patients remained hospitalized solely to complete a remdesivir treatment course. Thus, reductions in hospital length of stay due to remdesivir reported in randomized trials may not occur in non-research settings. Furthermore, the findings from the N3C report showed wide variation in remdesivir usage and may reflect clinicians' uncertainty regarding the net benefit of remdesivir when including costs and complexity of intravenous administration. These 2 observational studies highlight the importance of educating clinicians and developing health system approaches to consistently implement research findings into clinical practice.

RATIONALE AND BACKGROUND

Individuals hospitalized with COVID-19 infection are at substantial risk of prolonged hospitalization, experiencing hypoxic respiratory failure, needing advanced airway support, developing end-organ damage, and dying. Remdesivir is a nucleotide analogue prodrug that inhibits viral RNA polymerases and is administered intravenously. While originally developed as a potential treatment for other viral infections including Ebola, it has shown in vitro activity against SARS-CoV-2.[13,14] Numerous randomized controlled trials of remdesivir have been completed. On October 22nd, 2020 the FDA approved remdesivir for the treatment of patients over age 12 and weighing more than 40 kg hospitalized with COVID-19.[15] As part of our living review and rapid response, we provide our fifth update with additional information on the clinical effectiveness and harms of remdesivir in adults with COVID-19.

Our original review mainly compared the effectiveness of remdesivir to placebo. Subsequent updates also assessed the comparative effectiveness of 10- versus 5-day courses of remdesivir, as well as the effect of remdesivir compared with placebo on mortality in subgroups of patients based on baseline respiratory/ventilation status. In this update we summarize information on remdesivir from two newly published RCTs by Ader et al (DisCoVeRy; sub-trial)[6] and Abd-Elsalam et al[5] alongside previous updates. We update previous analyses and certainty of evidence (COE), and conduct cumulative meta-analyses, where feasible. Additionally, we also report on results of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance.

DATA SOURCES, SEARCHES, AND PLANNED UPDATES

We searched MEDLINE; Cochrane Central Trials Register (CENTRAL); World Health Organization (WHO) COVID-19 Database; National Institutes of Health (NIH) COVID-19 iSearch Portfolio; clinicaltrials.gov; tables of contents of the JAMA Network, the Lancet, and New England Journal of Medicine; and FDA and company websites from January 1st, 2020 through October 19th, 2021. Search terms included remdesivir and terms synonymous with COVID-19 (Supplemental Table 2). This is the fifth and final update of this living rapid review. Updates were based on weekly literature searches. New evidence that did not substantially

change review conclusions or certainty of evidence was summarized every 3 months. New evidence that substantially changed review conclusions was incorporated into major updates. We consider this a major update of the previously published fourth update.

DATA ABSTRACTION, QUALITY ASSESSMENT, EVIDENCE CERTAINTY, AND ANALYTIC METHODS

Study, population, disease severity, and intervention characteristics were extracted by 1 individual and verified by a second. We used a modification of the Cochrane Risk of Bias tool[16] to assess study risk of bias and GRADE to assess overall certainty of evidence for critical outcomes: mortality, clinical improvement, hospital length of stay, and harms (Supplemental Table 3).[17] We did not include studies rated high risk of bias in aggregate certainty of evidence ratings. We defined *a priori* thresholds for determining effect magnitude.

DATA SYNTHESIS AND ANALYSIS

From the new RCT we include data on viral clearance, mortality, new need for mechanical ventilation and hospital length of stay.[5] The new sub-trial DisCoVeRy (sub-trial of Solidarity) provided data on percent recovered, hospital length of stay, time to clinical improvement, proportion on mechanical ventilation or ECMO at follow-up, and adverse events.[6] Both studies compared a remdesivir 10-day course to SC in hospitalized patients with all severities of COVID-19. For outcomes which 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 individuals. For outcomes not reported by Solidarity (proportion recovered, proportion on ventilation at follow-up, and adverse events), we included data of all DisCoVeRy patients in our main analyses. There are no new data on percent with clinical improvement, percentage of patients hospitalized between days 7-14, time to recovery, or subgroup mortality data based on baseline respiratory support. We report below our decisions guiding earlier data synthesis and analysis processes.

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 <5 trials and a random-effects model (Hartung–Knapp–Sidik–Jonkman) when ≥5 trials reported on the outcome. Data were analyzed in R (R Foundation).[18]

We include updated meta-analyses, incorporating data from the newly published RCTs for the outcomes of mortality (all severity COVID-19), proportion recovered, proportion on 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, non-clinical outcome, we include this information to address uncertainty regarding the effect of remdesivir on viral clearance and the potential implications on use of remdesivir based on COVID-19 symptom duration.

Our primary analyses, decided upon in consultation with the American College of Physicians (ACP) Scientific Medical Policy Committee (SMPC), focused on comparing a 10-day course of remdesivir to a combined placebo and SC control for patients with any severity of COVID-19 for

all outcomes. We also provide results for the different controls (placebo and SC) separately and COEs for outcomes we were unable to pool. We conducted sensitivity analyses by baseline COVID-19 severity and combining remdesivir 10-day with 5-day course.

SUMMARY OF EVIDENCE AND ADDITIONAL CONSIDERATIONS

This version of our report includes 7 RCTs and 2 sub-trials (Figure 1). Two RCTs compared remdesivir IV (up to 10-day treatment duration) to placebo[7,11] and 2 open-label trials compared remdesivir for up to 10 days with SC.[5,12] Two open-label trials assessed 5- versus 10-day remdesivir treatment,[8,10] and 1 of these studies also included a third SC arm.[10] One open-label trial only compared 5-day remdesivir to SC.[9] Four trials were rated low risk of bias,[5,7,10,11] 2 were rated as moderate risk of bias,[8,12] and 1 was rated high risk of bias.[9]

All 7 RCTs enrolled adults hospitalized with COVID-19. Five trials included patients with severe COVID-19, typically defined as hospitalized individuals with 1 or more of the following criteria: radiographic infiltrates by imaging, oxygen saturation ≤94% on room air, tachypnea (respiratory rate >24 breaths per minute without supplemental oxygen), or requiring supplemental oxygen or mechanical ventilation. However, Goldman et al (SIMPLE-1) excluded patients requiring invasive mechanical ventilation or ECMO.[8] The Solidarity trial enrolled hospitalized adults regardless of COVID severity; however, their disease severity categories did not completely align with other RCTs, or with NIH definitions.[12] One trial (the 3-arm study) limited enrollment to hospitalized individuals with radiographic infiltrates and oxygen saturation on room air >94% (moderate severity).[10] Mahajan included patients with severe COVID-19 but those needing invasive mechanical ventilation at study entry were excluded.[9] The newest RCT by Abd-Elsalam reported a mean baseline oxygen saturation of 88.5% (without a report on level of oxygen supplementation), which is consistent with both NIH and WHO definitions of severe COVID-19.[5] Across all studies, patients were approximately 60 years of age, with most being male and white race. Studies excluded patients who were pregnant or had severe renal or hepatic dysfunction. In 4 RCTs, primary outcome was time to clinical improvement or symptom recovery, defined according to an ordinal scale that included death and use of supplemental oxygen or mechanical ventilation. The primary outcome in Solidarity was in-hospital all-cause mortality through 29 days.[12] The primary outcome in the study by Mahajan et al was clinical status from day 12 to 24, ranging from hospital discharge to increasing levels of oxygen support to death.[9] Detailed information about study characteristics, outcomes, and harms are reported in Supplemental Tables 3-8 and risk of bias in Supplemental Table 9. Definitions of disease severity are provided in Supplemental Table 10.

We also identified 2 studies that did not meet eligibility criteria but provide important contextual information from national databases on the use of remdesivir. Thus, we elected to describe their findings. One large retrospective cohort study was conducted of adults hospitalized with laboratory-confirmed COVID-19 in 123 Veterans Health Administration (VHA) hospitals between May 1 to October 8, 2020.[19] Due to lack of randomization, this study was not eligible for inclusion in the synthesis of evidence effectiveness and harms, but provides valuable information relevant to outcomes experienced among Veterans treated at VHA hospitals.

This study evaluated mortality and time to hospital discharge among hospitalized patients receiving remdesivir (n=1172) to propensity-matched controls (n=1172). Remdesivir recipients and matched controls were similar with regard to demographic characteristics, dexamethasone use, and severity of COVID-19. Remdesivir treatment was not associated with 30-day mortality (12.2% in remdesivir group vs 10.6% in controls; log rank P = .26; adjusted hazard ratio [HR], 1.06; 95% CI, 0.83-1.36). Furthermore, remdesivir recipients had a longer median time to hospital discharge compared with matched controls (6 days [interquartile range, 4-12 days] vs 3 days [interquartile range, 1-7 days]; P < .001). In addition to a clustering of hospital discharges in both groups at ≥14 days, discharge clustering occurred on days 5 and 6 for patients receiving remdesivir and days 1-4 in controls. This suggests that patients may have remained hospitalized primarily to complete the prescribed course of remdesivir. Study limitations included the potential for residual confounding, the low percentage of female patients (6.1%), the lack of information on phase of illness as measured by time since infection or duration of symptoms, and the limited number of patients with severe disease in the propensity matched cohort (approximately 20% were in intensive care units and 5% on invasive ventilation at matching).

One other retrospective study was published after our search but used the National COVID Cohort Collaborative (N3C) to characterize the use of remdesivir, hydroxychloroquine, and dexamethasone among individuals hospitalized with COVID-19 at 43 primarily academic health systems nationwide from February 1, 2020 to February 28, 2021.[20] Among 137,870 persons hospitalized with COVID-19 overall, 29,272 (21.2%) received remdesivir, 8754 (6.3%) hydroxychloroquine, and 53,909 (39.1%) dexamethasone. There was marked variation in use of remdesivir across health systems (intraclass correlation coefficient 84.6%). Remdesivir use was greatest among patients who were older, male, non-Hispanic White, or obese and those with more severe COVID-19 or comorbid illness. Use also varied over time, increasing from May through November 2020, consistent with emerging efficacy data[7,8] and guideline recommendations from the National Institutes of Health. Since November 2020, remdesivir use mostly plateaued with 27% of those hospitalized in February 2021 receiving the drug. The study did not separately report remdesivir use among persons with and without need for mechanical ventilation.

KEY FINDINGS (THRESHOLDS FOR SMALL, MODERATE, AND LARGE EFFECT PROVIDED IN TABLE 2 FOOTNOTES)

Summary (Tables 1 and 2, Figures 2 and 3)

All-Cause Mortality

- Overall, remdesivir may result in little to no difference in mortality versus placebo/SC control (RR: 0.94, [0.79 to 1.12]; ARD: -0.7%, [-2.4% to 1.0%]; 5 RCTs).
- Remdesivir's effect on mortality may vary by baseline oxygen requirements based on pooled post-hoc subgroup analyses. Remdesivir versus placebo/SC:
    - may result in little to no mortality difference in patients not requiring supplemental oxygen (RR: 0.78, [0.41 to 1.50]; ARD: -0.5%; [-0.2% to 0.8%]; 3 RCTs);

  - may result in small mortality reduction among patients receiving supplemental oxygen but who are not mechanically ventilated (RR: 0.81, [0.68 to 0.96]; ARD: -2.3%, [-4.2% to -0.4%]; 3 RCTs); and
  - may result in modest mortality increase in patients receiving mechanical ventilation or ECMO (RR: 1.19, [0.98 to 1.46]; ARD: 4.9%, [-0.6% to 10.3%]; 3 RCTs).

- Remdesivir's effect on mortality may not vary by other patient, disease, or treatment factors including age, gender, race/ethnicity, current smoking status, comorbidities, geographic location, presence of bilateral pulmonary infiltrates, concomitant corticosteroid use, duration of hospitalization prior to randomization (0, 1, ≥2 days),[12] or symptom duration (≤10 days vs >10 days).[11]

Non-mortality Outcomes

- Overall, remdesivir 10-day course probably results in a small reduction in proportion on mechanical ventilation or ECMO at follow-up versus placebo or SC (RR: 0.74, [0.62 to 0.89]; ARD: -4.5%, [-7.2% to -1.7%]; 4 RCTs).
- Remdesivir 10-day course probably results in little to no difference in new need for ventilation (invasive or non-invasive mechanical ventilation, or ECMO) versus SC in patients not ventilated at baseline (range of ARDs 0.4% to 3.0%; 2 RCTs).
- Remdesivir 10-day course compared with placebo or SC probably results in a moderate improvement in percent recovered (ARD: 6.5%, [3.0 to 10.0%]; 4 RCTs) or clinically improved (Range of ARDs: 7.2% to 7.5%; 2 RCTs).
- Remdesivir compared with placebo or SC may result in a large reduction in time to recovery for patients with severe disease, and an uncertain reduction in time to recovery for patients with moderate disease. Remdesivir may result in a small reduction in median time to clinical improvement versus control.
  - The effect of remdesivir on time to recovery may not vary by age categories, gender, symptom duration (≤10 days vs >10 days or median duration <9 days vs >9 days),[7,11] disease severity (mild/moderate vs severe [including critical]), or concomitant corticosteroid use.[7] However, in patients with severe disease who are receiving invasive mechanical ventilation or ECMO at baseline (*ie*, critical COVID-19) remdesivir may not reduce time to recovery.
- Remdesivir 10-day course may result in up to a moderate reduction in hospital length of stay vs control ; 4 RCTs). Remdesivir did not reduce the percentage hospitalized versus SC at day 7 (69% vs 59%) or day 14 (22% vs 19%) (1 RCT).
- Results from 3 RCTs found that remdesivir did not reduce viral clearance rates as compared to controls (placebo or SC).[6,11,21]
- Remdesivir may lead to a small reduction in serious adverse events versus SC or placebo by a moderate amount (ARD: -2.1%, [-6.5% to 2.2%]; 6 RCTs). Serious adverse events reported in trials included a combination of clinical findings resulting from COVID-19 progression (*eg*, respiratory failure and need for endotracheal intubation) and remdesivir side effects.

- Remdesivir may result in a small increase in any adverse events (ARD 4.9%, [-7.3% to 17.1%]; 5 RCTs).
- Compared with 10 days, a 5-day remdesivir course may reduce mortality and increase recovery and clinical improvement by small to moderate amounts, may reduce time to recovery, and may reduce serious adverse events among hospitalized patients not requiring mechanical ventilation.
    - For adults with room air baseline oxygen saturation >94%, a 5-day course of remdesivir compared to SC may improve recovery, reduce mortality, and decrease serious adverse events by a small amount.
- While findings were considered insufficient, results from 1 small post-hoc analysis (SIMPLE-1, n=66) found that among patients whose symptoms worsened and required mechanical ventilation or ECMO despite a 5-day course of remdesivir, continued treatment through 10 days resulted in lower mortality (ARD: 2.3%, [1.0% to 4.5%]).
- Pregnant women and patients with severe renal and hepatic dysfunction were excluded from trials. Therefore, findings may not apply to these individuals. The FDA advises caution in use among pregnant women and patients with an eGFR <30 mL/min.
- The FDA reports that infusion-related reactions and elevated liver transaminases have been observed in clinical studies with remdesivir.
- The FDA recommends clinicians assess kidney and hepatic function at baseline and during treatment. Remdesivir should be discontinued if alanine aminotransferase (ALT) levels increase to ≥5 times the upper limit of normal or any ALT elevation is accompanied by signs or symptoms of liver inflammation, or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR).
- The manufacturer will charge governments in the developed world, including the US government's Indian Health Services and the Department of Veterans Affairs, $2,340 for a 5-day course of remdesivir. US insurers, in addition to Medicare and Medicaid, will pay $3,120 for a 5-day treatment course ($520/vial). The price for those without insurance will be $390/vial.[22]
- Treating most individuals for 5 days may provide greater benefits and fewer harms, with lower drug costs, than a 10-day course, and would increase availability of limited drug supplies.

Figure 1. Literature Flow Diagram

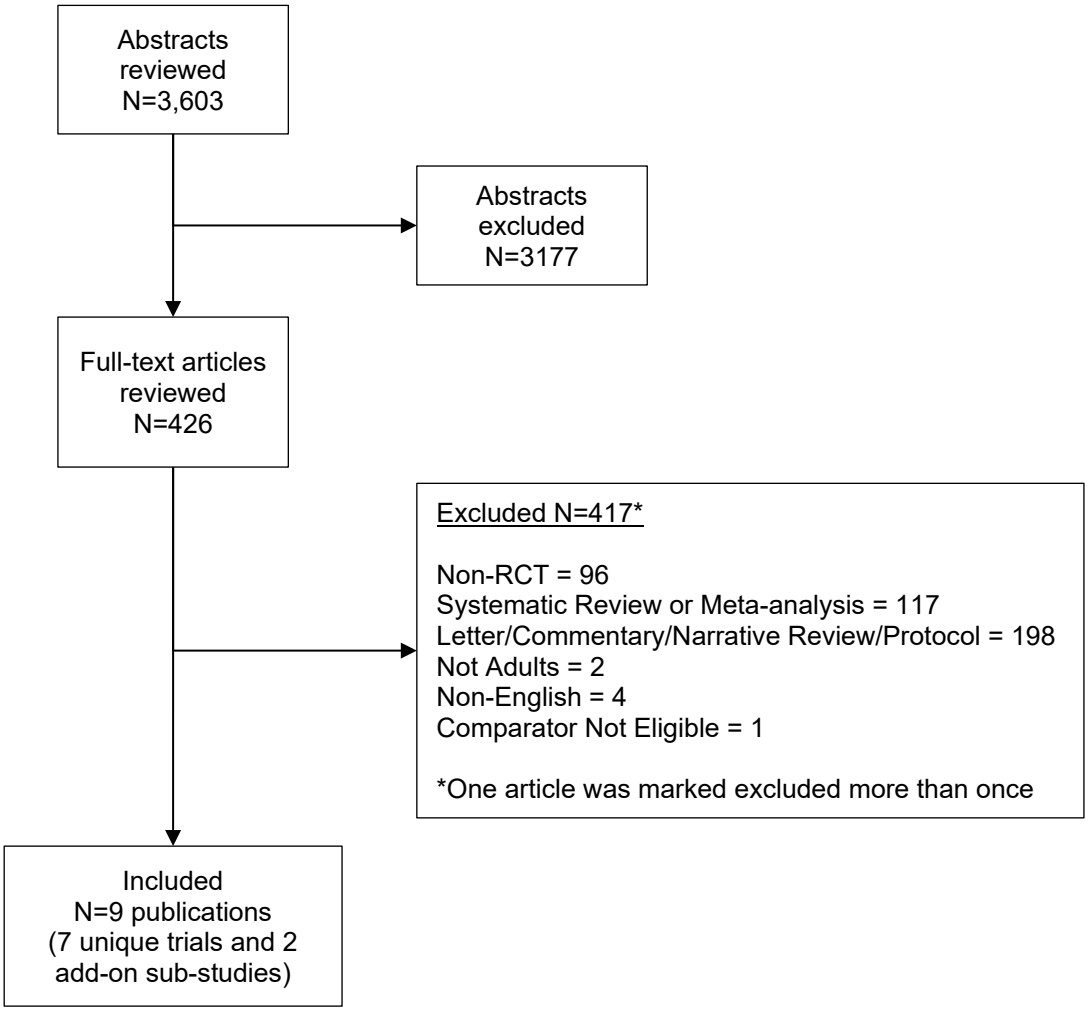


Table 1. Summary of Conclusions and Updated Findings for Randomized Trials of Remdesivir

Comparison	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 RCTs and 2 sub-studies of RCTs (n=7772 unique patients randomized)[5-7,10-12,21]	Mortality	Remdesivir 10-d course probably results in little to no difference vs control	1 new RCT[5] vs SC	Updated results confirm remdesivir 10-d course probably results in little to no difference vs control[5,7,10-12]
	Proportion recovered*	Remdesivir 10-d course probably results in a moderate increase in percent recovered vs control	Results from 1 sub-trial vs SC[6]	Updated results confirm remdesivir 10-d course probably results in a moderate increase in percentage recovered vs control[6,7,10,11]
	Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase in percentage with clinical improvement vs control[10,11]	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[5] and results from 1 sub-trial,[6] 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[5-7,11]
	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[7,10]	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 sub-trial vs SC[6]	Updated results confirm remdesivir 10-d course may result in a small reduction in time to clinical improvement vs control[6,11]
	Proportion on ventilation or ECMO at follow-up	Remdesivir 10-d course may result in a small reduction vs control	Results from 1 sub-trial vs SC[6]	Remdesivir 10-d course probably results in a small reduction vs control[6,7,10,11]

Comparison	Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
	Proportion with new need for ventilation	Remdesivir 10-d course probably results in little to no difference vs control	1 new RCT vs SC[5]	Updated results confirm remdesivir 10-d course probably results in little to no difference vs control[5,12]
	Serious adverse events	Remdesivir 10-d course probably results in a moderate reduction vs control	1 new RCT[5] and results from 2 sub-trials,[6,21] all vs SC	Remdesivir 10-d course may result in a small reduction vs control[6,7,10,11,21]
Remdesivir 10-day course vs placebo; 2 RCTs, any severity COVID-19 (n=1299 randomized)[7,11]	Mortality	Remdesivir 10-d course may result in a small reduction vs placebo[7,11]	No new evidence	No change in conclusions
	Proportion recovered*	Remdesivir 10-d course probably results in a moderate increase vs placebo[7,11]	No new evidence	No change in conclusions
	Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase vs placebo[11]	No new evidence	No change in conclusions
	Hospital length of stay	Remdesivir 10-day course may result in a moderate reduction vs placebo[7,11]	No new evidence	No change in conclusions
	Time to recovery	Remdesivir 10-day course may result in a large reduction vs placebo[7,11] *Subgroup analyses (prespecified):* Time to recovery did not vary by age, gender, symptom duration (≤10 days vs >10 days) 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[11]	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-d course may result in a moderate reduction vs placebo[7,11]	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 10-d course probably results in a moderate reduction vs placebo[7,11]	No new evidence	No change in conclusions

Comparison	Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
Remdesivir 10-day course vs SC, any severity COVID-19; 3 RCTs and 2 sub-trials of RCTs (n=6473 unique patients randomized)[5,6,10,12,21]	Mortality	Remdesivir 10-d course probably results in little to no difference vs SC	1 new RCT[5]	Updated results confirm remdesivir 10-d course probably results in little to no difference vs SC[5,10,12]
	Proportion recovered*	Remdesivir 10-d course may result in a moderate increase in percentage recovered vs SC	Results from 1 sub-trial[6]	Updated results confirm remdesivir 10-d course probably results in a moderate increase in percentage recovered vs SC[6,10]
	Proportion with clinical improvement†	Remdesivir 10-d course may result in a moderate increase in percentage clinically improved vs SC[10]	No new evidence	No change in conclusions
	Hospital length of stay	No evidence	1 new RCT[5] and results from 1 sub-trial[6]	Insufficient COE[5,6]
	Percent hospitalized	The percentage of patients hospitalized between days 7 and 14 did not differ between the remdesivir 10-d course and SC groups[10,12]	No new evidence	No change in conclusions
	Time to recovery	Insufficient COE[10]	No new evidence	No change in conclusions
	Time to clinical improvement	No evidence	Results from 1 sub-trial[6]	Insufficient COE[6]
	Proportion on ventilation or ECMO at follow-up	Remdesivir 10-d course may result in a small reduction vs SC	Results from 1 sub-trial[6]	Updated results confirm remdesivir 10-d course may result in a small reduction vs SC[6,10]
	Proportion with new need for ventilation	Remdesivir 10-d course probably results in little to no difference vs SC	1 new RCT[5]	Updated results confirm remdesivir 10-d course probably results in little to no difference vs SC[5,12]
	Serious adverse events	Remdesivir 10-d course may result in a small reduction vs SC	1 new RCT[5] and results from 2 sub-trials[6,21]	Updated results found remdesivir 10-d course may

Comparison	Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
				result in in little to no difference vs SC[5-7,10,11,21]
Remdesivir 5-day course vs SC 2 RCTs (n=481 randomized), **moderate**[10] **and severe COVID-19**[9]	Mortality	Remdesivir 5-d course may result in a small reduction vs SC[9,10]	No new evidence	No change in conclusions
	Proportion recovered*	Remdesivir 5-d course may result in a moderate increase vs SC[10]	No new evidence	No change in conclusions
	Proportion with clinical improvement†	Remdesivir 5-d course may result in a moderate increase vs SC[10]	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did not differ between the remdesivir 5-d course and SC groups[10]	No new evidence	No change in conclusions
	Time to recovery	Remdesivir 5-day course may result in a small reduction vs SC[9,10]	No new evidence	No change in conclusions
	Time to clinical improvement	NR		
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-day course may result in a small reduction vs SC[10]	No new evidence	No change in conclusions
	Proportion with new need for ventilation	Insufficient CoE, based on 1 RCT[9] 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[10]	No new evidence	No change in conclusions
Remdesivir 5-day course vs Remdesivir 10-day course, moderate[10] **and severe**[8] **COVID-19 (excludes critical COVID-19)** 2 RCTs (n=798 randomized)	Mortality	Remdesivir 5-d course may result in a small reduction vs 10-d course[8,10]	No new evidence	No change in conclusions
	Proportion recovered*	Remdesivir 5-d course may result in a moderate increase vs 10-d course[8,10]	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[8,10]	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did	No new evidence	No change in conclusions

Comparison	Outcome	Prior Conclusions	New Trial Results/ Analyses	Updated Conclusions
		not differ between the remdesivir 5-d and 10-d course groups[10]		
	Time to recovery	Remdesivir 5-d course may result in a small reduction vs 10-d course[8,10]	No new evidence	No change in conclusions
	Time to clinical improvement	NR		
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-d course may result in a small reduction vs 10-d course[8,10]	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 5-d course may result in a moderate reduction vs 10-d course[8,10]	No new evidence	No change in conclusions

Abbreviations. COE=certainty of evidence; ECMO=extracorporeal membrane oxygenation; NR=not reported; SC=standard of care
* Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only[7] or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care[8,10,11] 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[6]
† 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[11] or as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital)[8,10].

Table 2. Effect of Remdesivir in Randomized Controlled Studies

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
All-cause mortality				
Remdesivir 10-d course vs placebo or standard of care; 5 RCTs (n=7342) [5,7,10-12]	11 days to 6 months Any severity - No O_2 at baseline 25%; Receiving O_2 or ventilation (non-invasive and invasive) at baseline 75%	10.5% (393/3735) vs 11.1% (401/3607) Pooled ARD -0.7% (-2.4 to 1.0)	Moderate ‡	Remdesivir 10-d course probably results in little to no difference in mortality vs placebo or standard care
Remdesivir 10-day course vs placebo; 2 RCTs (n=1298)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13%	10.9% (59/541) vs14.8% (77/521) ARD -3.9% (-7.9 to 0.1)	Low §	Remdesivir 10-d course may result in a small reduction in mortality vs placebo Range of ARDs -3.9% to 1.1%
	Wang 2020[11]; 28 days Severe - No O_2 1%	13.9% (22/158) vs 12.8% (10/78) ARD 1.1% (-8.1 to 10.3)		
Remdesivir 10-d course vs standard of care; 3 RCTs (n=5844)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 84%	1.0% (2/193) vs 2.0% (4/200) ARD-1.0% (-3.4 to 1.4)	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% (-1.7 to 1.0)
	Solidarity 2020[12]; 28 days (*reported only during initial hospitalization; follow-up ceased after discharge*) Severe - No O_2 24%	11.0% (301/2743) vs 11.2% (303/2708) ARD -0.2% (-1.9 to 1.5)		
	Abd-Elsalam 2021[5]; 6 months O_2 at baseline NR. Noted as "mild to moderate symptoms".	9.0% (9/100) vs 7.0% (7/100) ARD 2% (-5.5 to 9.5)		
Remdesivir 5-day course vs standard of care; 2 RCTs (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 82%	0% (0/191) vs 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low‖	Remdesivir 5-d course may result in a small reduction in mortality vs SC
	Mahajan 2021[9]; 24 days Severe - No O_2 0%	Per protocol (day 12 to 24) 14.7% (5/34) vs 8.3% (3/36)		

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
		ARD 6.4% (-8.6 to 21.3)		
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14%	8.0% (16/200) vs 10.7% (21/197) ARD -2.7% (-8.4 to 3.1)	Low ¶	Remdesivir 5-d course of may result in a small reduction in mortality vs 10-d course Range of ARDs -2.7% to -1.0%
	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 86%	0% (0/191) vs 1.0% (2/193) ARD -1.0% (-2.8 to 0.7)		
Proportion of patients recovered, defined as discharge from the hospital or hospitalization for infection control purposes only[7] or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care[8,10,11] or discharge from the hospital, with or without limitations on activities[6]				
Remdesivir 10-d course vs placebo or standard of care; 4 RCTs (n=2514)[6,7,10,11]	28-29 days Any severity - No O_2 24%; Any O_2/Ventilation 76%	73.0% (948/1298) vs 66.8% (812/1216) Pooled ARD 6.5% (3.0 to 10.0)	Moderate ‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs placebo or standard care
Remdesivir 10-d course vs placebo; 2 RCTs (n=1289)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13%	73.8% (399/541) vs 67.6% (352/521) ARD 6.2% (0.7 to 11.7)	Moderate ‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs placebo Range of ARDs 6.2% to 7.0%
	Wang 2020[11]; 28 days Severe - No O_2 1%	70.7% (106/150) vs 63.6% (49/77) ARD 7.0% (-6.0 to 20.0)		
Remdesivir 10-d course vs standard of care; 2 RCTs (n=1225)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 28 days Moderate - No O_2 84%	92.2% (178/193) vs 85% (170/200) ARD 7.2% (1.0 to 13.5)	Moderate ‡	Remdesivir 10-d course probably results in a moderate increase in percentage recovered vs standard care Range of ARDs 6.4% to 7.2%
	Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1%	64% (265/414) vs 57.7% (241/418) ARD 6.4% (-0.3 to 13.0)		
Remdesivir 5-day course vs standard of care;	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 28 days Moderate - No O_2 82%	91.6% (175/191) vs 85% (170/200) ARD 6.6% (0.3 to 12.9)	Low §	Remdesivir 5-d course may result in a moderate increase

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
1 RCT(n=391)				in percentage recovered vs standard care
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 86%	64.5% (129/200) vs 53.8% (106/197) Baseline-adjusted ARD 6.3% (-2.8 to 15.4) 73.8% (141/191) vs 68.4% (132/193) ARD 5.4% (-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 two-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 [11] as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital) [8,10]				
Remdesivir 10-d course vs placebo[11] or standard of care[10]; 2 RCTs (n=629)	Wang 2020[11]; 28 days Severe - No O_2 1% Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 28 days Moderate - No O_2 84%	65.2% (103/158) vs 57.7% (45/78) ARD 7.5% (-5.7 to 20.7) 90.2% (174/193) vs 83% (166/200) ARD 7.2% (0.5 to 13.8)	Low §	Remdesivir 10-d course may result in a moderate increase in percentage with clinical improvement vs placebo or standard care Range of ARDs 7.2% to 7.5%
Remdesivir 5-day course vs standard of care; 1 RCT (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 28 days Moderate - No O_2 82%	89.5% (171/191) vs 83% (166/200) ARD 6.5% (-0.3 to 13.3)	Low §	Remdesivir 5-d course may result in a moderate increase in percentage with clinical improvement vs standard care
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 86%	64.5% (129/200) vs 54.3% (107/197) Baseline-adjusted ARD 6.5% (-2.8 to 15.7) 70.2% (134/191) vs 65.3% (126/193) ARD 4.9% (-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 Length of Stay (LOS), Days (Median IQR)				

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-d course vs control; 4 RCTs (n=2331)[5-7,11]	*See individual study results below*	Outcome not pooled, difference in medians ranged from 6 to -2 days shorter in LOS	Low **	Remdesivir 10-d may result in up to a moderate reduction in LOS vs placebo or standard care
Remdesivir 10-d course vs placebo; 2 RCTs (n=1299)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13% Wang 2020 [11]; 28 days Severe - No O_2 1%	*Initial hospitalization* 12 (6 to 28) vs 17 (8 to 28) MD -5 days [95% CI, -7.7 to -2.3] 25 (16 to 38) vs 24 (18 to 36) MD 0 days (-4.0 to 4.0)	Low ††	Remdesivir 10-d course may result in a moderate reduction in LOS vs placebo
Remdesivir 10-d course vs standard care 2 RCTs (n=1032)	Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1% Abd-Elsalam 2021[5]; 6 months O_2 at baseline NR. Noted as "mild to moderate symptoms".	15 (10 to 29) vs 13 (8 to 29) HR 0.94 (0.80 to 1.11) 10 (8 to 13.8) vs 16 (12 to 21)	Insufficient ‡‡	
Percent hospitalized				
Remdesivir 10-d course vs standard of care	Solidarity[12], Severe - No O_2 24%; No differences in percent hospitalized at 7 (69% vs 59%) and 14 days (22% vs 19%) SIMPLE-2[10], Moderate - No O_2 84%: No differences in percent hospitalized at 11 (34% vs 38%) and 14 days (23% vs 31%).			
Remdesivir 5-day course vs standard of care	SIMPLE-2[10], Moderate - No O_2 82%: No differences in percent hospitalized at 11 (30% vs 38%) and 14 days (23% vs 31%),			
Remdesivir 5-day course vs Remdesivir 10-d course	SIMPLE-2[10], Moderate - No O_2 86%: No differences in percent hospitalized at 11 (30% vs 34%) and 14 days (23% vs 23%)			
Time to Recovery, Days, Median (IQR)				

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-d course vs placebo or standard of care; 2 RCTs (n=2506) [7,10]	11-29 days Any severity - No O_2 38%; Any O_2/Ventilation 62%	Difference in medians ranged from 5 to -1 days 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 standard care
Remdesivir 10-d course vs placebo; 1 RCT(n=1062)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13%	10 (95% CI 9 to 11) vs 15 (95% CI 13 to 18); P<.001 Rate ratio 1.29 (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 days vs >10 days) or disease severity)*[7]
Remdesivir 10-d course vs standard of care; 1 RCT (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 84%	8 (4 to 13) vs 7 (4 to 15); HR 1.11 (0.90 to 1.37)	Insufficient ‡‡	
Remdesivir 5-day course vs standard of care; 2 RCTs (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 82%	6 (5 to 10) vs 7 (4 to 15); HR 1.18 (0.96 to 1.45)	Low ‖	Remdesivir 5-d course may result in a small reduction in time to recovery vs standard care
	Mahajan 2021[9]; Day 10 through Day 20 Severe - No O_2 0%	Data NR Trialists noted patients in both groups "had an equal time to recovery (not defined) between 10 and 20 days."		
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14%	10 (6 to 18) vs 11 (7 to not able to estimate); P NS HR 0.81 (0.64 to 1.04)	Low ¶	Remdesivir 5-d course may result in a small reduction in time to recovery vs 10-d course
	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days	6 (5 to 10) vs 8 (4 to 13); HR NR		

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
	Moderate - No O_2 86%			
Time to Clinical Improvement, Days, Median (IQR)				
Remdesivir 10-d course vs placebo or standard of care; 2 RCTs (n=1069)[6,11]	11-29 days Severe - No O_2 1%	Difference in medians ranged from 2 to -1 days 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 standard care
Remdesivir 10-d course vs placebo; 1 RCT (n=237)	Wang 2020[11]; 28 days Severe - No O_2 1%	21 (13 to 28) vs 23 (18 to 36); HR 1.23 (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 standard of care; 1 RCT (n=832)	Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1%	12 (8 to 24) vs 11 (7 to 26) HR 0.92 (0.79 to 1.08)	Insufficient ‡‡	Remdesivir 10-d course may result in an uncertain effect on time to clinical improvement vs standard care
Proportion on ventilation or ECMO at follow-up (Spinner on day 11, Wang on day 14 and ACTT-1 and DisCoVeRy on day 15)				
Remdesivir 10-d course vs placebo or standard of care; 4 RCTs (n=2518)[6,7,10,11]	11 – 15 days Any severity - No O_2 24%; Any O_2/Ventilation 76%	12.5% (162/1301) vs 17.3% (211/1217) Pooled ARD -4.5% (-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 standard care
Remdesivir 10-d course vs placebo; 2 RCTs (n=1299)	Beigel (ACTT-1) 2020[7] Severe - No O_2 13% Wang 2020[11] Severe - No O_2 1%	17.6% (95/541) vs 23.2% (121/521) ARD -5.7% (-10.5 to -0.8) 2.6% (4/153) vs 9.0% (7/78) ARD -6.4% (-13.2 to 0.5)	Low §	Remdesivir 10-d course may result in a moderate reduction in proportion on invasive ventilation or ECMO at follow-up vs placebo Range of ARDs -5.7% to -6.4%
Remdesivir 10-d course vs standard of care;	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10] Moderate - No O_2 84%	0.5% (1/193) vs 2.0% (4/200) ARD -1.5% (-3.7 to 0.7)	Low §	Remdesivir 10-d course may result in a small reduction in proportion on invasive

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
2 RCTs (n=1225)	Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1%	15.0 % (62/414) vs 18.9% (79/418) ARD -3.9% (-9.0 to 1.2)		ventilation or ECMO at follow-up vs standard care Range of ARDs -3.9% to -1.5%
Remdesivir 5-day course vs standard of care; 1 RCT (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10] Moderate - No O_2 82%	0% (0/191) vs 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low §	Remdesivir 5-d course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up vs standard care
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8] Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020[10] Moderate - No O_2 86%	8.0% (16/200) vs 16.8% (33/197) ARD -8.8% (-15.2 to -2.3) 0% (0/191) vs 0.5% (1/193) ARD -0.5% (-1.9 to 0.9)	Low ¶	Remdesivir 5-d course may result in a small reduction in proportion on 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, ie, severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
Subsequent need for ventilation (invasive or non-invasive ventilation, or ECMO) in those not ventilated at baseline				
Remdesivir 10-d course vs standard of care; 2 RCTs (n=5164)[5,12]	Solidarity 2020[12]; 28 days Severe - No O_2 24% Abd-Elsalam 2021[5]; 6 months O_2 at baseline NR. Noted as "mild to moderate symptoms".	11.9% (295/2489) vs 11.5% (284/2475) ARD 0.4% (-1.4 to 2.2) 11.0% (11/100) vs 8.0% (8/100) ARD 3.0% (-5.1 to 11.1)	Moderate ‡	Remdesivir 10-d course probably results in little to no difference in new need for ventilation vs standard care Range of ARDs 0.4% to 3.0%

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course vs standard of care; 1 RCT (n=70)[9]	Day 12 through Day 24 Severe - No O_2 0%	11.8% (4/34) vs 5.6% (2/36) ARD 6.2% (-7.0 to 19.4)	Insufficient §§	
Serious Adverse Events (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-d course vs placebo or standard of care; 6 RCTs (n=2627)[5-7,10,11,21]	11-29 days Any severity - No O_2 24%; Any O_2/Ventilation 76%	21.8% (312/1428) vs 24.6% (344/1499) Pooled ARD -2.1% (-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 RCTs (n=1299)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13% Wang 2020[11]; 28 days Severe - No O_2 1%	24.6% (131/532) vs 31.6% (163/516) ARD -7.0% (-12.4 to -1.5) 18.1% (28/155) vs 25.6% (20/78) ARD -7.6 (-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 standard of care; 4 RCTs (n=1546)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 84% Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1% Barratt-Due (NOR-Solidarity) 2021[21]; 90 days O_2 at baseline NR (Overall, Solidarity severe) Abd-Elsalam 2021[5]; 6 months O_2 at baseline NR. Noted as "mild to moderate symptoms"	5.2% (10/193) vs 9.0% (18/200) ARD -3.8% (-8.9 to 1.2) 33.3% (135/406) vs % 31.1% (130/418) ARD 2.2% (-4.2 to 8.5) 19.0% (8/42) vs 14.9% (13/87) ARD 4.1% (-9.9 to 18.1) 0% (0/100) vs 0% (0/100) ARD 0% (-1.9 to 1.9)	Low ††	Remdesivir 10-d course may result in in little to no difference in serious adverse events vs standard care 20.6% (153/741) vs 20.0% (161/805) Pooled ARD -0.2% (-1.95 to 1.5)

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course vs standard of care; 1 RCT (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 82%	4.7% (9/191) vs 9.0% (18/200) ARD -4.3% (-9.3 to 0.7)	Low §	Remdesivir 5-d course may result in a small reduction in serious adverse events vs standard care
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 86%	21.0% (42/200) vs 34.5% (68/197) ARD -13.5% (-22.2 to -4.8) 4.7% (9/191) vs 5.2% (10/193) ARD -0.5% (-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, ie, 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 standard of care; 5 RCTs (n=2627)[6,7,10,11,21]	11-29 days Any severity - No O_2 24%; Any O_2/Ventilation 76%	58.8% (781/1328) vs 55.7% (724/1299) Pooled ARD 4.9% (-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 RCTs (n=1281)	Beigel (ACTT-1) 2020[7]; 29 days Severe - No O_2 13% Wang 2020[11]; 28 days Severe - No O_2 1%	57.3% (305/532) vs 62.6% (323/516) ARD -5.3% (-11.2 to 0.7) 65.8% (102/155) vs 64.1% (50/78) ARD 1.7 (-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 standard of care;	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 84%	58.5% (113/193) vs 47% (93/200) ARD 12.0% (2.2 to 21.9)	Low ††	Remdesivir 10-d course may result in a moderate increase

Comparison(s); Number of trials (number evaluated)	Study, Year; Assessment timepoint; Disease severity, based on oxygen (O_2) - status at admission	Absolute effect of Remdesivir vs Control (95% CI)	Certainty of Evidence	Summary
3 RCTs (n=393)	Ader (DisCoVeRy) 2021[6]; 29 days Severe - No O_2 1% Barratt-Due (NOR-Solidarity) 2021[21]; 90 days O_2 at baseline NR (Overall, Solidarity severe)	59.4% (241/406) vs 56.5% (236/418) ARD 2.9% (-3.8 to 9.6) 47.6% (20/42) vs 25.3% (22/87) ARD 22.3% (4.7 to 40.0)		in any adverse events vs standard of care 58.3% (374/641) vs 49.8% (351/705) Pooled ARD 7.3% (2.0 to 12.6)
Remdesivir 5-day course vs standard of care; 1 RCT (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020[10]; 11 days Moderate - No O_2 82%	51.3% (98/191) vs 46.5% (93/200) ARD 4.8% (-5.1 to 14.7)	Low §	Remdesivir 5-d course may result in a small increase in any adverse events vs standard care
Remdesivir 5-day course vs Remdesivir 10-d course; 2 RCTs (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020[8]; 14 days Severe - No O_2 14%	70.5% (141/200) vs 73.6% (145/197) ARD -3.1% (-11.9 to 5.7)	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%

Abbreviations. ARD = Absolute risk difference; CI = Confidence intervals; HR=Hazard ratio; IQR = inter quartile range; MD=Mean difference; NR= Not reported; NS = Not statistically significant; RCT = Randomized controlled trial

*** GRADE Working Group grades of evidence**
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Explanations for Certainty of Evidence assessment

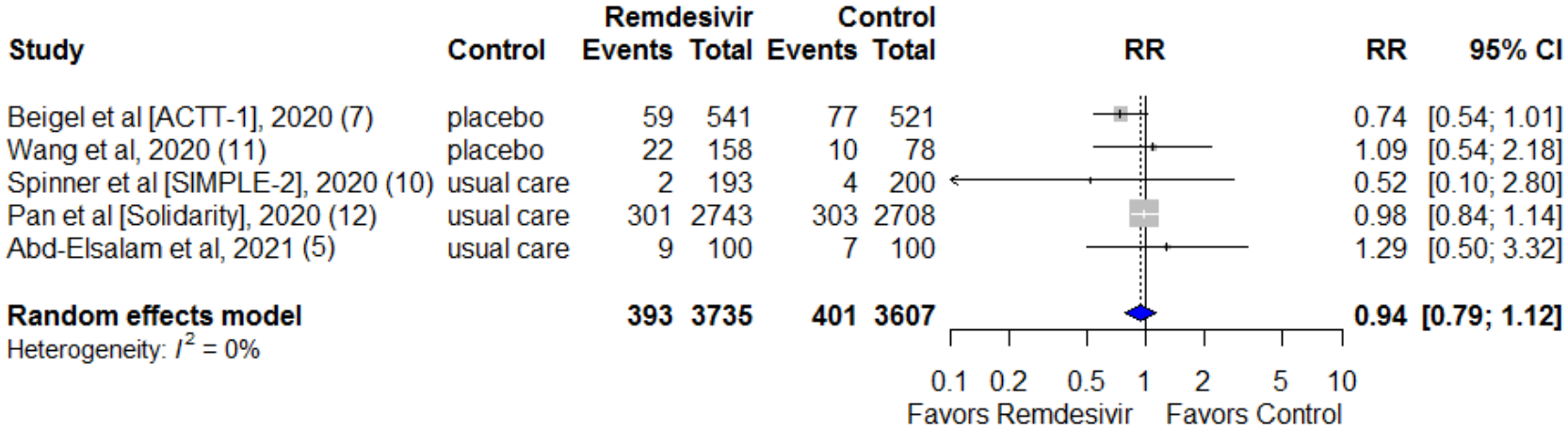
† Thresholds for determining magnitude by outcome are as follow:
All-cause mortality: Little or No effect <1%; Small effect 1-2.9%; Moderate effect 3-4.9%; Large effect ≥5%
Recovery: Little or No effect <2%; Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Clinical Improvement: Little or No effect <2% Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Length of Stay: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days
Time to Recovery or Clinical Improvement: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days

Invasive 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 (5), assessed as high risk of bias, did not impact 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)

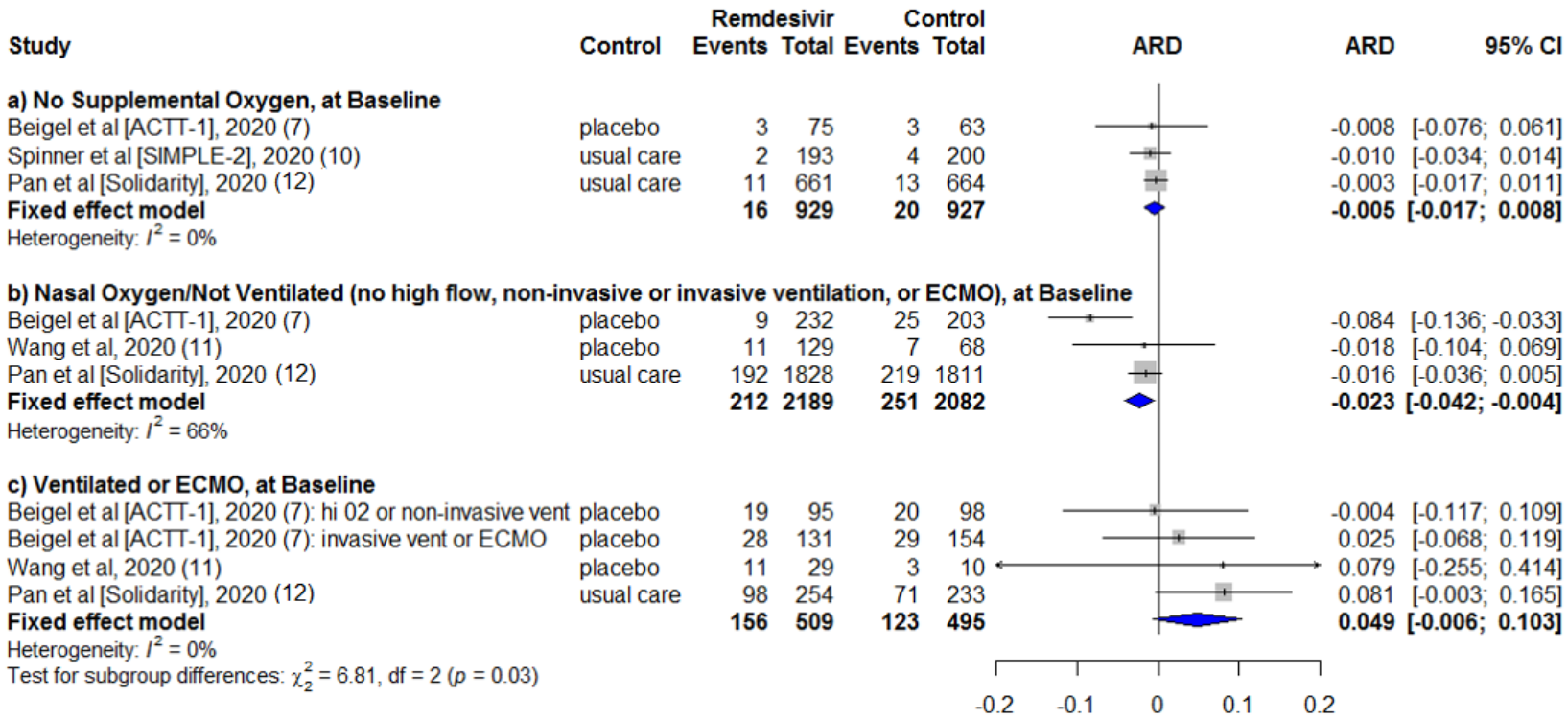
Figure 2. Mortality, Remdesivir 10-Day Course versus Control (Placebo or Standard of Care)

2a. Overall



Abbreviations. CI=confidence interval; RR=risk ratio

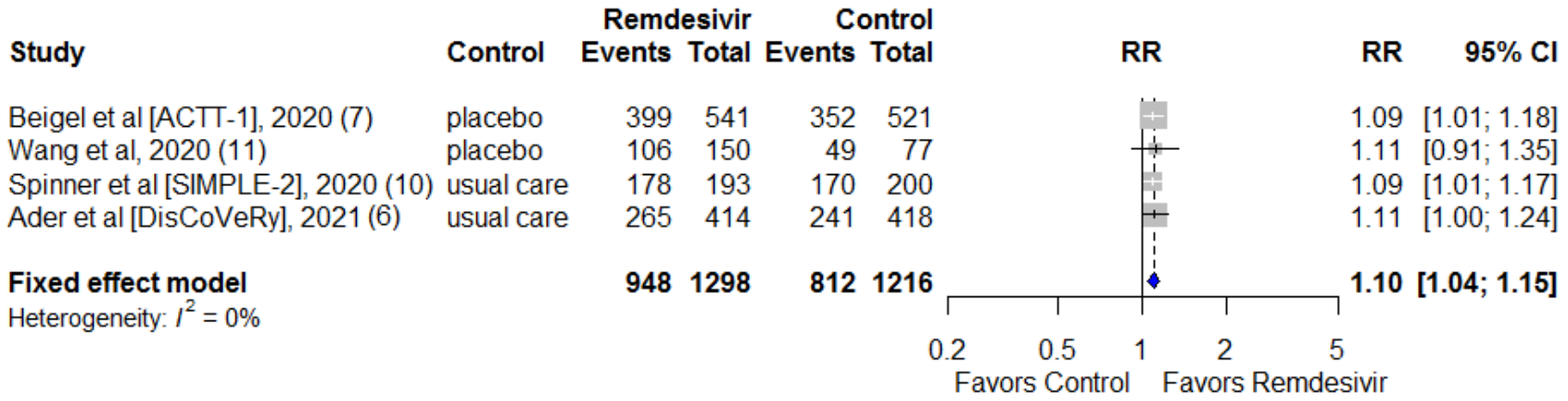
2b. Results by Initial Respiratory Status



Abbreviations. CI=confidence interval; ECMO=extracorporeal membrane oxygenation; RR=risk ratio
Blue diamond reflects pooled results from trials (listed above) that enrolled patients in the corresponding respiratory support subgroups.

Figure 3. Non-Mortality Outcomes, Remdesivir 10-Day Course versus Control (Placebo or Standard of Care)

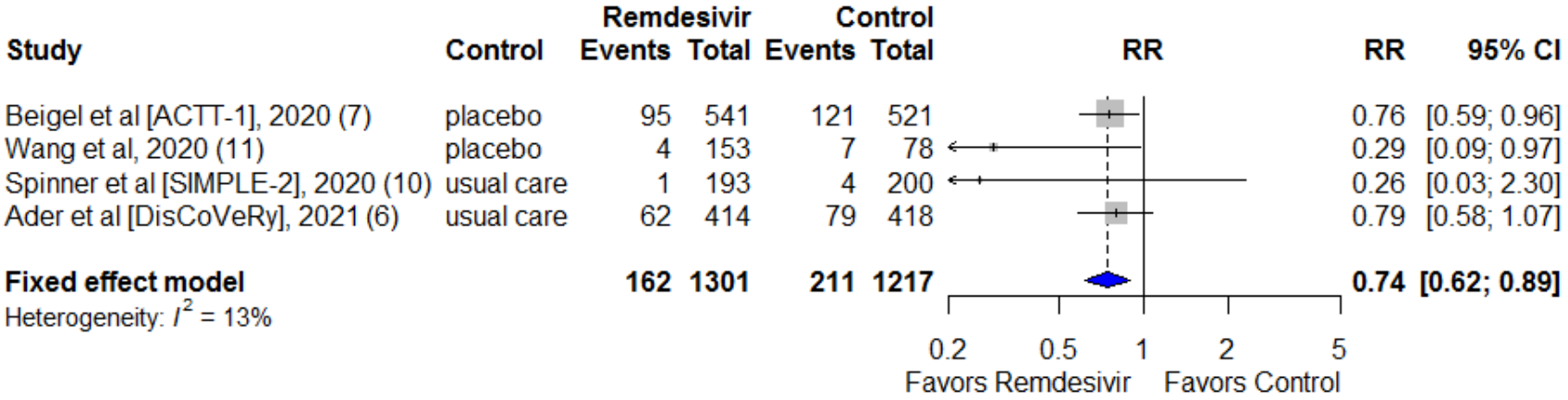
3a. Proportion of Patients Recovered



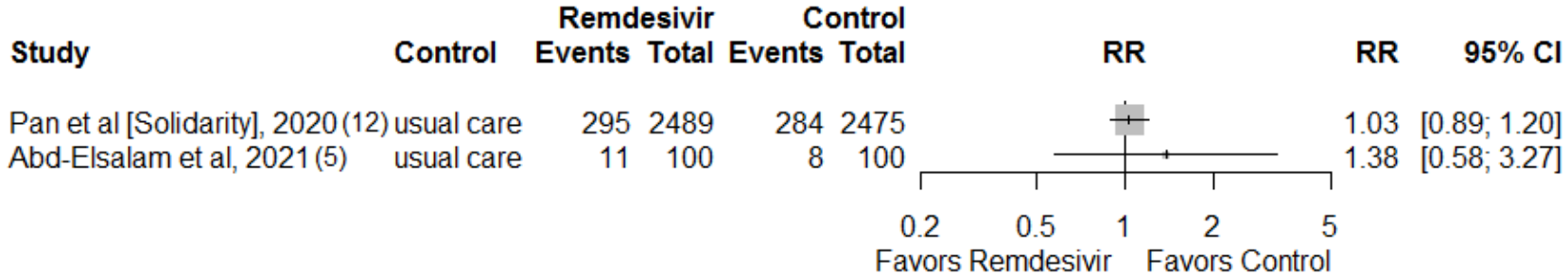
Abbreviations. CI=confidence interval; RR=risk ratio

3b. Need for Invasive Ventilation/ECMO

Proportion receiving ventilation/ECMO at follow-up



Subsequent need for ventilation

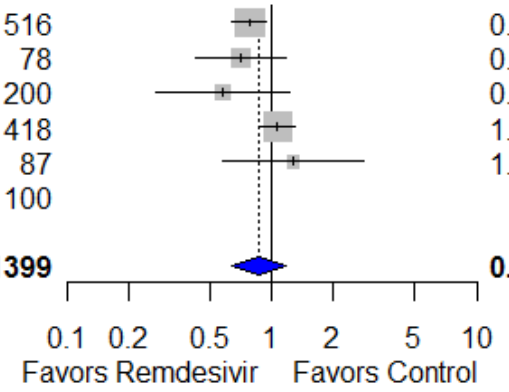


Abbreviations. CI=confidence interval; ECMO=extracorporeal membrane oxygenation; RR=risk ratio
* For the pooled trials, defined as: proportion on invasive ventilation/ECMO (new vs continued from baseline) at follow up (ACTT-1 on day 15, Wang on day 14, and SIMPLE-2 on day 11).
† Unpooled Solidarity trial, defined as: subsequent need for ventilation in those not ventilated at baseline (through day 28)

3c. Patients with ≥1 Serious Adverse Event

Study	Control	Remdesivir Events	Remdesivir Total	Control Events	Control Total	RR	RR	95% CI
Beigel et al [ACTT-1], 2020 (7)	placebo	131	532	163	516		0.78	[0.64; 0.95]
Wang et al, 2020 (11)	placebo	28	155	20	78		0.70	[0.43; 1.17]
Spinner et al [SIMPLE-2], 2020 (10)	usual care	10	193	18	200		0.58	[0.27; 1.22]
Ader et al [DisCoVeRy], 2021 (6)	usual care	135	406	130	418		1.07	[0.88; 1.30]
Barratt-Due et al [NOR-Solidarity], 2021 (16)	usual care	8	42	13	87		1.27	[0.57; 2.84]
Abd-Elsalam et al, 2021 (5)	usual care	0	100	0	100			
Random effects model		**312**	**1428**	**344**	**1399**		**0.87**	**[0.64; 1.18]**

Heterogeneity: I^2 = 50%



Abbreviations. CI=confidence interval; RR=risk ratio

SUMMARY OF INDIVIDUAL STUDIES

WANG (SEVERE COVID-19) 2020[11]

Design: Double-blind, multicenter, randomized, placebo-controlled trial in Hubei, China.

Intervention: Remdesivir (n=158) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions.

Comparator: Placebo (n=79).

Patients: Nonpregnant adults (n=237) with COVID-19 and hospitalized within 12 days of symptom onset with pneumonia confirmed by chest imaging, oxygen saturation of ≤94% on room air, or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300 mm Hg (Severe COVID-19). Baseline characteristics: median ages: 64-66 years; percent male: 59%; race: Asian 100%; median symptom duration: 11 days; on invasive ventilation: 10%.

Risk of Bias: Low. Stopped early (enrolled 237 of the intended 453 patients) due to stated control of the COVID-19 outbreak in Hubei and inability to identify and recruit additional eligible patients.

Primary Outcome: Time to clinical improvement up to day 28, defined as the time from randomization to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital.

Main Results: In adults hospitalized for COVID-19 and evidence of lower respiratory tract infection, a 10-day course of remdesivir, as compared with placebo, resulted in a nonsignificant increase in the percentage of patients with clinical improvement at day 28 (65.2% (103/158) vs 57.7% (45/78); ARD 7.5% [-5.7 to 20.7]) and a decrease in the median time to clinical improvement (21 [13 to 28] vs 23 days [15 to 28]; hazard ratio (HR) 1.23 [0.87 to 1.75]). Information was also available to develop a recovery outcome defined as: “discharge from the hospital or hospitalized but not requiring supplemental oxygen” (items 1 and 2 on the 6-point ordinal scale). Remdesivir resulted in a non-significant increase in the percentage of patients recovered at day 28 versus placebo (70.7% (106/150) vs 63.6% (49/77); ARD 7.0% [-6.0 to 20.7]). Remdesivir as compared with placebo did not significantly reduce median length of hospital stay (25 vs 24 days, mean difference 0.0 days [-4.0 to 4.0]), need for invasive mechanical ventilation (8.2% vs 12.8%; ARD -4.6% [-13.2 to 4.0]), or mortality at 28 days (13.9% (22/158) vs 12.8% (10/78); ARD 1.1% [-8.1 to 10.3]). The effectiveness of remdesivir on mortality and time to clinical improvement did not vary by symptom onset duration (≤10 days vs >10 days). There was a non-significant moderate reduction in serious adverse events in patients on remdesivir as compared with placebo (18.1% (28/155) vs 25.6% (20/78); ARD -7.6% [-19.0 to 3.9]). Measures of viral load or undetectable viral RNA in sputum or naso/oropharyngeal swabs by day 28 did not differ between remdesivir compared with placebo.

BEIGEL (ACTT-1: MODERATE AND SEVERE COVID-19) 2020: FINAL REPORT[7]

Design: Randomized, double-blind, multinational, adaptive placebo-controlled trial.

Intervention: Remdesivir (n=538) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusion.

Comparator: Placebo (n=521).

Patients: Nonpregnant adults (n=1063) hospitalized for COVID-19 with evidence of pneumonia and reduced oxygen levels but without severe hepatic or renal impairment or requiring mechanical ventilation at study entry (Severe COVID-19). Baseline characteristics: age (mean): 59 years; race: 53% white; percent male: 64%; median symptom duration: 9 days; on invasive ventilation or ECMO: 27%.

Risk of Bias: Low.

Primary Outcome: Time to recovery defined as the first day, during the 28 days of enrollment, on which a patient satisfied categories 1, 2, or 3 on an 8-point ordinal scale (1=not hospitalized, no limitations of activities; 2=not hospitalized, limitation of activities, home oxygen requirement, or both; 3=hospitalized not requiring supplemental oxygen and no longer requiring medical care). The original primary outcome was "change in the difference in clinical status". Soon after study enrollment trial statisticians, unaware of treatment assignment or outcomes, proposed a change in the primary outcome from "difference in clinical status" based on the 8-category scale to time to recovery.

Main Results: Patients randomized to remdesivir received up to 10-days of treatment or until hospital discharge. Among individuals with complete compliance data available, a 10-day course was used in 38.4% of individuals and 41.2% received less than 10 doses because they recovered and were discharged from the hospital. Compared with placebo, remdesivir resulted in a shorter time to recovery (median 10 days [9 to 11] vs 15 days [13 to 18]; rate ratio for recovery 1.29 [1.12 to 1.49]). Remdesivir increased the percentage of patients recovered (73.8% (399/541) versus 67.6% (352/521), ARD 6.2% [0.7 to 11.7]). Remdesivir resulted in a numerically lower mortality at 29 days (10.9% (59/541) versus 14.8% (77/521), ARD -3.9% [-7.9 to 0.1]; HR for death 0.73 [0.52 to 1.03]). Remdesivir did significantly reduce need for invasive mechanical ventilation on day 15 compared with placebo (17.6% vs 23.2%; ARD -5.7% [-10.5 to -0.8]). Remdesivir reduced serious adverse events compared with placebo (24.6% (131/532) versus 31.6% (163/516); ARD -7% [-12.4 to -1.5]). There was a moderate but non-significant reduction in any adverse events with remdesivir compared with placebo (ARD -5.3% [-11.2 to 0.7]). The effectiveness of remdesivir in shortening time to recovery did not vary by prespecified subgroups of age (categories), sex, symptom duration (≤10 days vs >10 days), or disease severity (mild/moderate or severe). However, in patients receiving invasive mechanical ventilation or ECMO at study entry (n=285, 27% of enrollees; critical severity COVID-19 as defined by NIH, WHO and FDA criteria), recovery was not improved with remdesivir (relative risk 0.98 [0.70 to 1.36]).

GOLDMAN (SIMPLE-1: SEVERE COVID-19) 2020[8]

Design: Randomized, open-label, multi-national, Phase 3, comparative effectiveness clinical trial.

Intervention: Remdesivir, 5-day course (n=200) 200 mg on day 1 followed by 100 mg on days 2–5 IV.

Comparator: Remdesivir, 10-day course (n=197) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Patients: Adults (n=397) hospitalized for COVID-19 with radiologic evidence of pneumonia and reduced oxygen levels (severe COVID-19) but did not require mechanical ventilation at study entry or have multiorgan failure or severe hepatic or renal impairment. Baseline characteristics: median age: 61-62 years; percent male: 64%; race: 70% white; median symptom duration: 8 days; receiving mechanical ventilation or ECMO: 4%. Patients randomized to the 10-day course had significantly worse clinical status at study entry than those randomized to the 5-day course (P=.02).

Risk of Bias: Moderate.

Primary Outcome: Clinical status on day 11 described as clinical improvement based on an improvement of 2 or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death.

Main Results: Patients randomized to the 10-day course had significantly worse clinical status at study entry than those randomized to the 5-day course (P=.020). After adjustment for baseline differences in clinical status, patients in the 10-day group had a clinical status distribution at day 14 similar to patients in the 5-day group (P=0.140). A 5-day course of remdesivir may result in a moderate increase in recovery at 14 days (defined as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing care) compared with a 10-day course (64.5% (129/200) vs 53.8% (106/197); baseline-adjusted ARD 6.3% [-2.8 to 15.4]) (low certainty). A small reduction in mortality was also observed at day 14 for a 5-day treatment course versus a 10-day (8.0% (16/200) vs 10.7% (21/197); ARD -2.7% [-8.4 to 3.1]) (low certainty). The percentage of individuals having clinical improvement was moderately higher with 5-day course treatment compared with a 10-day course (64.5% (129/200) vs 54.3% (107/197); baseline-adjusted ARD -6.5% [−15.7 to 2.8]) (low certainty). A 5-day course of remdesivir may result in a moderate reduction in need for mechanical ventilation (8.0% vs 16.8%; ARD -8.8% [-15.2 to -2.3]) and a small reduction in median time to recovery versus a 10-day course (10 days (IQR 6 to 18) vs 11 days (IQR: 7 to not able to estimate); HR 0.81 [0.64 to 1.04]). Numerically, more patients in the 5-day group than in the 10-day group were discharged from the hospital (120/200, 60% vs 103/197, 52.3%; ARD 7.7% [-2.0 to 17.4]). In post-hoc analyses, treatment beyond 5 days among patients who were receiving noninvasive positive pressure ventilation or high-flow oxygen, low-flow oxygen, or breathing ambient air did not improve outcomes. However, among patients who progressed to require mechanical ventilation or ECMO at day 5, mortality was higher in the 5-day group compared with the 10-day group (40.0% (10/25) vs 17.1% (7/41); ARD 22.9% [0.5 to 45.3]). In post-hoc analyses based on pooling of data across remdesivir treatment duration arms, the percentage of patients discharged from the hospital was numerically

higher among individuals who received remdesivir within 10 days of symptom onset compared with those treated after more than 10 days of symptoms (62% vs 49%). Compared with patients randomized to the remdesivir 10-day course, the 5-day course may result in a large reduction in serious adverse events (21.0% (42/200) versus 34.5% (68/197); ARD -13.5% [-22.2 to -4.8]) and may result in a small reduction in any adverse events.

SPINNER (SIMPLE-2: MODERATE COVID-19) VERSUS STANDARD OF CARE 2020[10]

Design: Randomized, open-label, multinational, Phase 3, comparative effectiveness clinical trial.

Intervention: Remdesivir, 5-day course (n=191) 200 mg on day 1 followed by 100 mg on days 2–5 IV.

Comparator (1): SC (n=200).

Comparator (2): Remdesivir, 10-day course (n=193) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Patients: Adults (n=582) hospitalized for COVID-19 with radiologic evidence of pneumonia without reduced oxygen levels on room air or severe hepatic or renal impairment. Baseline characteristics: median age: 56-58 years; percent male: 61%; race: 58% white; median symptom duration: median 8-9 days; receiving mechanical ventilation or ECMO: 0%.

Risk of Bias: Low.

Primary Outcome: Clinical improvement defined as an improvement of 2 or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death.

Main Results: A 5-day course of remdesivir as compared with SC may result in a greater percentage of individuals with recovery (defined as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing care) at day 28 (91.6% (175/191) vs 85% (170/200); ARD 6.6% [0.3 to 12.9]) (low certainty) and clinical improvement at day 28 (89.5% (171/191) vs 83% (166/200); ARD 6.5% [-0.3 to 13.3]) (low certainty). Clinical improvement was similar in the 5-day versus 10-day arms (ARD 5%) and greater with 10-day versus SC arms (ARD 7%) (low certainty). Deaths were infrequent in each group (insufficient certainty). A 5-day course of remdesivir may result in a small reduction in median time to recovery versus SC (6 days [IQR 5 to 10] vs 7 days [IQR: 4 to 15]; HR 1.18 [0.96 to 1.45] (low certainty). There may be small to no differences between the 5-day course and SC or a 10-day course in serious adverse events (4.7% (9/191) vs 9.0% (18/200); ARD -4.3% [-9.3 to 0.7] and 4.7% (9/191) vs 5.2% (10/193), ARD 0.5 [-4.8 to 3.9]), respectively) (low certainty). There may be a moderate increase in any adverse event with a 10-day course compared with SC (58.5% (113/193) versus 46.5% (93/200); ARD 12.0% [2.2 to 21.9]) (low certainty).

WHO SOLIDARITY TRIAL CONSORTIUM (SOLIDARITY: MODERATE AND SEVERE COVID-19) VERSUS STANDARD OF CARE 2020[12]

Design: Randomized, open-label, multinational, Phase 3, comparative effectiveness clinical trial.

Intervention: Remdesivir, 10-day course (n=12743) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Comparator: SC (n=2708).

Patients: Adults (n=5472) hospitalized for COVID-19. Baseline characteristics: Age >50: 65%; Male: 63%; Race: NR; median symptom duration: NR days; receiving invasive or noninvasive ventilation or ECMO: 9%.

Risk of Bias: Low, publication presents interim results only.

Primary Outcome: In-hospital 28-day overall mortality.

Main Results: Compared with SC, remdesivir did not reduce in-hospital 28-day mortality overall (11.0% (301/2743) versus 11.2% (303/2708); ARD -0.2 [-1.9 to 1.5]). Remdesivir did not reduce the subsequent need for ventilation (invasive or non-invasive mechanical ventilation, or ECMO) in those not ventilated at baseline (11.9% (295/2489) vs 11.5% (284/2475); ARD 0.4% [-1.4 to 2.2]) and did not decrease the percentage of individuals hospitalized at day 7 (69% vs 59%) or day 14 (22% vs 19%). Remdesivir's mortality effect did not differ by age, sex, current smoking status, comorbidities, country of origin, bilateral pulmonary infiltrates, corticosteroid use, duration of hospitalization prior to randomization, or respiratory support at baseline (though there was a suggestion of increased mortality with remdesivir in those ventilated at entry (HR 1.20, [0.80 to 1.80]).

NOR-SOLIDARITY[21]

Design: Add-on sub-study of WHO Solidarity, randomized, open-label, 23 Norwegian hospitals, comparative effectiveness clinical trial.

Intervention: Remdesivir, 10-day course (n=43) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Comparator: SC (n=58). For harms n=87 (some participants receiving SC acted as controls for both remdesivir and a hydroxychloroquine arm, whereas some patients receiving SC served as a control for only 1 of the active treatment arms).

Patients: Adults (N=101) hospitalized with any severity of COVID-19 in 23 Norwegian hospitals. Baseline characteristics: Mean age: 59 years; Male: 73%; Race: NR; mean symptom duration: 7 days; receiving invasive or noninvasive ventilation or ECMO: NR; admitted to ICU: 4%.

Risk of Bias: Low.

Sub-study-specific Outcomes: Viral clearance as assessed by SARS-CoV-2 polymerase chain reaction (PCR) in oropharyngeal specimens, degree of respiratory failure, and inflammatory variables. While NOR-Solidarity was not designed or adequately powered to address clinical outcomes, the authors also provided clinical efficacy outcomes not previously reported by WHO Solidarity, specifically mortality at days 28 and 60, admission to ICU during hospitalization, and time to receipt of mechanical ventilation.

Main Results: Remdesivir did not alter viral clearance compared to SC; results did not vary by symptom duration. Patients on remdesivir, as compared to SC, did not differ with regards to 28-day mortality (2.4% vs 5.3%), or 60-day mortality (7.1% vs 5.3%) with an estimated marginal risk difference of 1.9% (95% CI -7.8 to 11.6). Admission to ICU during hospitalization [19.0% vs 19.3%; estimated marginal risk difference of -0.3% (95% CI -15.9 to 15.4)] and time to receipt of mechanical ventilation [HR 1.3 (0.5 to 3.4)] also did not differ between the remdesivir and SC groups. More patients in the remdesivir group reported at least 1 adverse event compared with SC (39% vs 25%). The number of patients with a serious adverse event was similar between the remdesivir and SC groups (19% and 15%, respectively). No patient in either group withdrew from the trial due to an adverse event.

MAHAJAN 2021[9]

Design: Randomized, open-label, Phase 3, comparative effectiveness clinical trial in Punjab, India.

Intervention: Remdesivir, 5-day course (n=41) 200 mg on day 1 followed by 100 mg on days 2–5 IV.

Comparator: SC (n=41).

Patients: Adults (n=70 per protocol participants) hospitalized for severe COVID-19. Baseline characteristics: Age 58: 65%; Male: 66%; Race: NR; median symptom duration: 6.8 days; receiving mechanical ventilation: 0%.

Risk of Bias: High.

Primary Outcome: Clinical status outcomes from day 12 to 24 ranging from hospital discharge to increasing levels of oxygen support to death reported as per-protocol analysis only. Patient's clinical status was assessed by physical examination and laboratory analyses on a 6-point ordinal scale.

Main Results: Compared with SC, remdesivir did not reduce per-protocol mortality (day 12 to 24, 14.7% (5/34) vs 8.3% (3/36); ARD 6.4% [-8.6 to 21.3]) or mortality based on the number of patients randomized (14.6% (6/41) vs 12.2% (5/41); ARD 2.4% [-12.3 to 17.2]. The trialists noted patients in both groups "had an equal time to recovery between 10 and 20 days" (data were not reported). Remdesivir did not reduce the subsequent need for mechanical ventilation compared with SC (11.8% (4/34) vs 5.6% (2/36); ARD 6.2% [-7.0 to 19.4]). Given the study's high risk of bias we did not include it in aggregate certainty of evidence.

DISCOVERY 2021[6]

Design: Sub-trial of WHO Solidarity, randomized, open-label, 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg), comparative effectiveness clinical trial. Forty-seven percent of the participants did not overlap with WHO Solidarity.

Intervention: Remdesivir, 10-day course (n=414) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Comparator: SC (n=418).

Patients: Adults (N=832) hospitalized with moderate (61%) or severe COVID-19 in 48 European sites. Baseline characteristics: Median age: 64 years; Male: 70%; Race: white 69%; median symptom duration: 9 days; receiving invasive or noninvasive ventilation or ECMO: 22%; admitted to ICU: 44%.

Risk of Bias: Low.

Sub-study-specific Outcomes: Clinical status at day 15 measured by the WHO 7-point ordinal scale, an outcome not reported by Solidarity. Additional new outcomes were time to improvement, length of hospitalization, proportion needing ventilation on day 15, any adverse event, serious adverse events, and SARS-CoV-2 kinetics.

Main Results: Compared with SC, remdesivir did not significantly improve clinical status on day 15 (odds ratio 0.98 [95% CI 0.77–1.25]). The results did not vary by age, sex, duration of symptoms, disease severity, or country of randomization. For all participants, there was no significant difference between remdesivir and SC in time to improvement (12 days [IQR 8 to 24] vs 11 days [IQR 7 to 26]; hazard ratio 0.92 [95% CI 0.79-1.08]), length of hospitalization, proportion needing ventilation on day 15 (15.0% (62/414) vs 18.9% (79/418); RR 0.79 [95% CI 0.85-1.07]), 28-day mortality (8.2% (34/414) vs 8.9% (37/418); odds ratio 0.93 [95% CI 0.57–1.52]), serious adverse events (33.3% (135/406) vs 31.1% (130/418); odds ratio 1.11 [95% CI 0.83–1.50]), or any adverse events (59.4% (241/406) vs 56.5% (236/418); odds ratio 1.14 [95% CI 0.86–1.50]). For patients unique to DisCoVeRy (n=392) (*ie*, those not previously included in Solidarity), remdesivir, as compared with SC, did not reduce 29-day mortality (8.2% vs 10.2%, P=0.51), but reduced the proportion of patients with subsequent need for ventilation or ECMO (15.7% vs 29.9%; P=0.002; personal communication with Dr. France Mentré). There was no effect of remdesivir on SARS-CoV-2 kinetics measured in the nasopharynx.

ABD-ELSALAM 2021[5]

Design: Randomized, open-label, comparative effectiveness clinical trial in Egypt.

Intervention: Remdesivir, 10-day course (n=105) 200 mg on day 1 followed by 100 mg on days 2–10 IV.

Comparator: SC (n=104).

Patients: Adults (N=209, 200 analyzed) hospitalized in Egypt with COVID-19. Baseline characteristics: Mean age: 53.5 years; Male: 60%; Race: NR; median symptom duration: unclear; receiving invasive or noninvasive ventilation or ECMO: NR; admitted to ICU: NR.

Risk of Bias: Low

Sub-study-specific Outcomes: Length of hospital stay and mortality. Additional outcomes included need for ventilation and adverse events.

Main Results: Compared with SC, remdesivir significantly reduced median duration of hospitalization (10 days vs 16 days; P<0.001) but did not reduce mortality (9% vs 7%; P=0.6).

Remdesivir did not affect the need for subsequent ventilation. No serious adverse events were noted in either group.

ONGOING STUDIES OR STUDIES COMPLETED AFTER OUR SEARCH DATE

As 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 an inhaled formulation of remdesivir and studies including previously excluded populations (pregnant women, children, and patients with renal dysfunction).[23] Additionally, 1 placebo-controlled RCT that evaluated remdesivir given intravenously daily for 3 days to high-risk unvaccinated outpatients with COVID-19 with symptoms for ≤ 7 day was published after our last search date.[24] The study enrolled patients through April 8, 2021, prior to the emergence of the delta or omicron variants of SARS-CoV-2 as the dominant strains. Remdesivir reduced the primary composite end point of COVID-19–related hospitalization or death at day 28 as compared to placebo (0.7% [2/279] vs 5.3% [15/283]; p=0.008). There were no deaths in either arm. The trial was terminated early due to "the changing epidemiology and adoption of additional treatment options at the time".[24] A total of 1.6% (4/246) patients in the remdesivir group and 8.3% (21/252) in the placebo group had a COVID-19–related medically attended visit by day 28 (HR, 0.19; 95% CI, 0.07 to 0.56). Any adverse event and a serious adverse event occurred in 42.3% and 1.8% of the patients in the remdesivir group and in 46.3% and 6.7% of those in the placebo group. The results of this study led, in part, to the FDA expanding its approval and emergency use authorization for 3 days of remdesivir in certain non-hospitalized adults and pediatric patients judged to be at high risk for the treatment of mild-to-moderate COVID-19 disease. Specifically, these include individuals with symptomatic mild-to-moderate confirmed COVID-19 for <7 days and at least 1 risk factor for progression to hospitalization including age ≥60 years, obesity (BMI ≥30), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, chronic liver disease, current cancer, and sickle cell disease. Patients who received, required, or were expected to require supplemental oxygen were excluded from the trial.[24]

Final results from Solidarity as well as additional sub-studies reporting single-country results may provide additional information.[12] The AAMMURAVID trial will evaluate remdesivir, dexamethasone, and baricitinib, using a factorial design.[25] Gilead Sciences is sponsoring an ongoing trial of remdesivir among participants with severely reduced kidney function who are hospitalized.[26] Another Gilead Sciences-sponsored trial evaluating an inhaled nebulized version of remdesivir in a small phase-1 trial is listed as complete on clinicaltrials.gov, but is not yet published.[27] There are small trials either ongoing or complete but not yet published in Bangladesh,[28] Pakistan,[29] and Iran.[30]

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