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REVIEW

Remdesivir for the Treatment of COVID-19: A Narrative Review

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ABSTRACT

Despite the wide availability of effective vaccines, COVID-19 continues to be an infectious disease of global importance. Remdesivir is a broad-spectrum antiviral and was the first US Food and Drug Administration-approved treatment for COVID-19. In clinical guidelines, remdesivir is currently the only recommended antiviral for use in hospitalized patients with COVID-19, with or without a supplemental oxygen requirement. It is also recommended for nonhospitalized patients with COVID-19 and hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who are at high risk of progression to severe disease. This narrative review explores the evidence for remdesivir across various clinical outcomes and evolution of clinical guidelines through a survey over time of randomized controlled trials, observational studies, and meta-analyses. Remdesivir, compared to standard of care, appears to improve survival and disease progression in a variety of patient populations with COVID-19 across a spectrum of disease severity and SARS-CoV-2 variant periods. Remdesivir also appears to improve time to clinical recovery, increase rate of recovery, and reduce time on supplemental oxygen and readmission rates. More recent large, real-world studies further support the early use of remdesivir in a range of patient populations, including those with immunocompromising conditions.

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PLAIN LANGUAGE SUMMARY

When people get sick with COVID-19, which is caused by the SARS-CoV-2 virus, treatment with an antiviral may be needed to prevent serious illness. Remdesivir is an antiviral and was the first US Food and Drug Administration-approved treatment for COVID-19. Studies have found that treating COVID-19 with remdesivir can save lives and keep patients from getting sicker. Remdesivir appears to help patients get better faster, need oxygen treatment for less time, and avoid having to go back to the hospital. Newer studies with patients treated in real-world settings, outside of controlled research environments, show that early treatment with remdesivir is likely to help many different groups of patients, including those with health conditions that weaken their body's ability to fight infection. Because of this research, guidelines recommend that remdesivir should be given to some patients with COVID-19 outside of the hospital and to those who need to stay in the hospital for COVID-19. Remdesivir should also be given to those who need to stay in the hospital for other reasons but have COVID-19 and a health condition that puts them at risk of serious illness.

Keywords: Antiviral therapy; COVID-19; Remdesivir; SARS-CoV-2; Real-world evidence; Clinical practice guidelines

Key Summary Points

Remdesivir is a broad-spectrum adenosine nucleotide analogue prodrug and the first US Food and Drug Administration-approved antiviral agent for the treatment of COVID-19.

Evolving guidelines recommend remdesivir for use in hospitalized and nonhospitalized patients with COVID-19, including those hospitalized for other reasons who test positive for SARS-CoV-2 infection.

Clinical trials, observational studies, and meta-analyses show that remdesivir, compared to standard of care, may improve survival and disease progression across various patient populations and levels of COVID-19 severity.

New and ongoing studies continue to support the early use of remdesivir for novel SARS-CoV-2 variants and in a variety of patient populations, including those with immunocompromising conditions.

INTRODUCTION

COVID-19 remains a high-priority infectious disease in the USA, with more than 100 million cases and more than 1.1 million deaths as of November 2023 [1]. Despite the wide availability of effective vaccines, only 17.0% of the US population has received an updated booster dose as of May 2023, eroding the long-term population-level protective effects of vaccination [1]. Furthermore, COVID-19 vaccine effectiveness wanes progressively over time, especially against the Omicron variant [2–4], and Omicron's global dominance has been associated with a dramatic rise of breakthrough infections in vaccinated individuals [5, 6], contributing to COVID-19's persistence as a major public health issue. COVID-19 variants of concern continue to evolve and potentially escape the immunity provided by current vaccines; this highlights both the necessity of continually updated vaccines and, because this process takes time, the need for effective treatments to mitigate the impact of severe disease.

Remdesivir is an adenosine nucleotide analogue prodrug with broad-spectrum antiviral activity against RNA viruses, including filoviruses, paramyxoviruses, and coronaviruses such as severe acute respiratory syndrome coronaviruses (SARS-CoV, SARS-CoV-2) and Middle East respiratory syndrome coronavirus [7, 8]. Remdesivir inhibits viral replication by stalling RNA-dependent RNA polymerase through delayed chain termination, which

results from the sterically impaired passage of the cyano group in the remdesivir ribose moiety at the + 3 position post incorporation [9, 10]. Remdesivir has been shown to be effective in treating hospitalized and nonhospitalized patients with COVID-19, and protection appears consistent over different SARS-CoV-2 variant periods [11–14].

Remdesivir received US Food and Drug Administration (FDA) Emergency Use Authorization for the treatment of COVID-19 on 1 May 2020 and became the first FDA-approved antiviral treatment for COVID-19 on 22 October 2020 [15, 16]. In clinical guidelines from the National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA), remdesivir is indicated for use in hospitalized and nonhospitalized patients with COVID-19 not requiring mechanical ventilation; its use is also indicated in individuals hospitalized for other reasons who test positive for SARS-CoV-2 infection and have risk factors for progression to severe disease (Table 1) [17, 18]. The World Health Organization (WHO) initially made a

Table 1 US guidelines for the use of remdesivir in adults as of June 2023; guidelines are subject to change

COVID-19 severity	NIH [17]	IDSA [18]
Nonhospitalized with mild-to-moderate COVID-19	RDV started within 7 days of symptom onset and given for 3 days is recommended in patients at high risk[a] of progression to severe disease	RDV started within 7 days of symptom onset and given for 3 days is recommended in patients at high risk[a] of progression to severe disease
Hospitalized for reasons other than COVID-19 with mild-to-moderate COVID-19	RDV started within 7 days of symptom onset and given for 3 days is recommended in patients at high risk[a] of progression to severe disease	RDV started within 7 days of symptom onset and given for 3 days is recommended in patients at high risk[a] of progression to severe disease
Hospitalized and does not require supplemental oxygen	RDV given for 5 days[b] is recommended in patients at high risk[a] of progression to severe disease	RDV started within 7 days of symptom onset and given for 3 days is recommended in patients at high risk[a] of progression to severe disease
Hospitalized and requires LFO	RDV given for 5 days plus dexamethasone is recommended in most patients[c]	RDV given for 5 days plus dexamethasone is recommended
Hospitalized and requires HFO or NIV	Clinicians may consider adding RDV to 1 of the recommended immunomodulator combinations (dexamethasone plus PO baricitinib or IV tocilizumab)	RDV given for 5 days plus dexamethasone is recommended
Hospitalized and requires IMV or ECMO	RDV is not recommended	RDV is not recommended

ECMO extracorporeal membrane oxygenation, *HFO* high-flow oxygen, *IDSA* Infectious Diseases Society of America, *IMV* invasive mechanical ventilation, *IV* intravenously administered, *LFO* low-flow oxygen, *NIH* National Institutes of Health, *NIV* noninvasive ventilation, *PO* orally administered, *RDV* remdesivir

[a]High-risk conditions include older age, a prolonged interval (e.g., > 6 months) since the most recent vaccine dose, and a decreased likelihood of an adequate immune response to vaccination due to a moderate-to-severe immunocompromising condition or receipt of immunosuppressive medications

[b]Or continued until hospital discharge, whichever comes first

[c]If these patients progress to requiring HFO, NIV, IMV, or ECMO, the full course of RDV should still be completed. RDV without dexamethasone can be used in patients with minimal oxygen requirements

conditional (weak) recommendation against the use of remdesivir based on the interim results of the Solidarity trial [19] but amended its guidelines following publication of the final analysis to support the use of remdesivir in patients with severe COVID-19 and in nonhospitalized patients with COVID-19 who are at risk of hospitalization [20–22]. On the basis of data through October 2021, the American College of Physicians concluded that remdesivir increases the proportion of patients experiencing recovery or clinical improvement and reduces length of stay (LOS) and time to clinical improvement [23].

Although remdesivir is currently the only antiviral with supportive data from patients hospitalized for COVID-19, other therapies have demonstrated efficacy for the treatment of nonhospitalized patients with COVID-19. Ritonavir-boosted nirmatrelvir (NIM-RTV) is an oral protease inhibitor approved by the FDA for the treatment of mild-to-moderate COVID-19 in adults at high risk of progression to severe COVID-19 [24]. In nonhospitalized adults with COVID-19, NIM-RTV was shown to reduce the risk of hospitalization or all-cause death by 89% compared to placebo [25], an efficacy similar to that of remdesivir (87%) in nonhospitalized patients [26]. Four monoclonal antibodies products (bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab) targeting the SARS-CoV-2 spike protein have received FDA Emergency Use Authorizations for the treatment of mild-to-moderate COVID-19 [27–30], as well as one (tixagevimab plus cilgavimab) for preexposure prophylaxis [31]. However, anti-SARS-CoV-2 monoclonal antibody activity can vary greatly across variants; because the dominant Omicron subvariants are not expected to be susceptible to these products, they are not authorized for use in the USA [17, 32].

This narrative review aims to survey the current literature for remdesivir to contextualize and underscore remdesivir's importance in the ongoing effort to manage COVID-19. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DISEASE PROGRESSION AND MORTALITY

Clinical trials for remdesivir are summarized in Table 2 [11, 12, 20, 33–36]. The NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT-1) was a double-blind, randomized, placebo-controlled trial of 10-day intravenously administered remdesivir in adults ($N = 1062$) hospitalized with confirmed SARS-CoV-2 infection and evidence of lower respiratory tract infection [11]. Patients receiving remdesivir had a shorter time to clinical recovery (primary endpoint) than those receiving placebo: median 10 days (95% CI 9–11) versus 15 days (95% CI 13–18) with a rate ratio for recovery of 1.29 (95% CI 1.12–1.49; $P < 0.001$); this benefit was greatest in patients randomized $\leq$ 10 days after symptom onset and when treatment was administered earlier during illness. Overall, all-cause mortality rates were 6.7% and 11.9% at day 15 for remdesivir and placebo, respectively (hazard ratio [HR], 0.55; 95% CI 0.36–0.83), and 11.4% and 15.2% at day 29 (HR 0.73; 95% CI 0.52–1.03). It is important to note that a subgroup analysis in patients on low-flow oxygen (LFO) yielded a statistically significant reduction of 70% in mortality for the remdesivir group at 29 days (HR 0.30; 95% CI 0.14–0.64). Although ACTT-1 was insufficiently powered to demonstrate benefit in subgroups, the 95% CIs overlapped across respiratory support subgroups, and testing for interaction revealed no treatment heterogeneity by respiratory support status, indicating that remdesivir's benefits might exist across subgroups, although the magnitude and clinical significance of these effects are likely to vary. Furthermore, because median recovery time could not be estimated for patients in the highest respiratory support category, follow-up time may have been too short to evaluate that subgroup. The 29% increased recovery rate for hospitalized patients receiving remdesivir versus placebo in ACTT-1 was the basis for FDA approval of remdesivir in October 2020 [17].

Solidarity was a large WHO-sponsored, international, open-label trial in adults hospitalized with COVID-19 who were randomized to

Table 2 Summary of clinical trials of remdesivir in adults

Study	Population	Recruitment period	Follow-up period	Patients	Countries/region	Intervention(s) and control	Outcomes
ACTT-1 [11]	Adults hospitalized with COVID-19[a] and evidence of LRTI	February–April 2020	28 days	1062 (mean age, 59 years; 36% female; 53% White)	USA, Denmark, UK, Greece, Germany, South Korea, Mexico, Spain, Japan, Singapore	(1) IV RDV (200 mg day 1; 100 mg days 2–10) (2) Placebo	Primary outcome •RDV reduced time to clinical recovery by 5 days vs placebo Secondary outcome •RDV reduced mortality at 29 days by 70% vs placebo in patients on LFO
WHO Solidarity, final report [20]	Adults hospitalized with COVID-19 (not laboratory confirmed)	March 2020–January 2021	Not specified	8275 (22% aged ≥ 70 years; 37% female)	Europe (15 countries), Latin America (5 countries), Asia (11 countries), Africa (4 countries)	Open label (1) IV RDV (200 mg day 1; 100 mg days 2–10) (2) SOC	Primary outcomes •RDV reduced in-hospital mortality in patients on supplemental oxygen •RDV did not significantly reduce mortality in patients requiring MV at baseline Secondary outcome •RDV reduced progression to initiation of MV

Table 2 continued

Study	Population	Recruitment period	Follow-up period	Patients	Countries/region	Intervention(s) and control	Outcomes
PINETREE [12]	Aged ≥ 12 years, hospitalized with COVID-19[a] and at high risk of disease progression	September 2020–April 2021	28 days	562 (mean age, 50 years; 48% female; 42% Hispanic/Latinx)	USA, Spain, Denmark, UK	(1) IV RDV (200 mg day 1; 100 mg days 2–3) (2) Placebo	Primary outcome •3-day RDV reduced risk of hospitalization or death by 87% vs placebo
Goldman et al. (GS-US-540-5773) [33]	Aged ≥ 12 years, hospitalized with COVID-19[a] and severe COVID-19 pneumonia[b]	March 2020	30 days	402 (median age, 62 years; 36% female; 70% White)	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	Open label (1) IV RDV (200 mg day 1; 100 mg days 2–5) (2) IV RDV (200 mg day 1; 100 mg days 2–10)	Primary outcome •Similar improvements in clinical status at day 14 were seen with 5- and 10-day RDV Secondary outcome •Similar rates of mortality, clinical recovery, and time to clinical improvement were seen in 5- and 10-day RDV arms
Spinner et al. (GS-US-540-5774) [34]	Aged ≥ 12 years, hospitalized with COVID-19[a] and moderate COVID-19 pneumonia[c]	March–April 2020	≥ 30 days	584 (median age, 57 years; 39% female; 58% White)	USA, UK, China, Taiwan, Japan, South Korea, Singapore, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland	Open label (1) IV RDV (200 mg day 1; 100 mg days 2–5) (2) IV RDV (200 mg day 1; 100 mg days 2–10) (3) SOC	Primary outcome •RDV for 5 days improved clinical status at 11 days vs SOC

Table 2 continued

Study	Population	Recruitment period	Follow-up period	Patients	Countries/region	Intervention(s) and control	Outcomes
CATCO [35]	Adults hospitalized with COVID-19[a]	August 2020–April 2021	60 days	1281 (median age, 66 years; 40% female; 41% White)	Canada	Open label (1) IV RDV (200 mg day 1; 100 mg days 2–10) (2) SOC	Primary outcome •RDV did not significantly reduce in-hospital mortality vs SOC Secondary outcome •Incident need for MV was 50% lower with RDV vs SOC
REDPINE [36]	Aged ≥ 12 years, eGFR < 30 mL/min/1.73 m^2, hospitalized for COVID-19[a] with severe COVID-19 pneumonia[b]	March 2021–March 2022	60 days	243 (mean age, 69 years; 43% female; 67% White; 37% with ESKD)	Brazil, Portugal, Spain, UK, USA	(1) IV RDV (200 mg day 1; 100 mg days 2–5) (2) Placebo	Primary outcome •At day 29, there was no significant difference in all-cause mortality or IMV for RDV vs placebo in individuals with moderate-to-severe renal insufficiency

ACTT-1 Adaptive COVID-19 Treatment Trial, *CATCO* Canadian Treatments for COVID-19, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *IMV* invasive mechanical ventilation, *IV* intravenously administered, *LFO* low-flow oxygen, *LRTI* lower respiratory tract infection, *MV* mechanical ventilation, *RDV* remdesivir, *SOC* standard of care, *WHO* World Health Organization

[a]Laboratory-confirmed COVID-19

[b]COVID-19 with pulmonary infiltrates and either receiving supplemental oxygen or oxygen saturation < 94% on room air

[c]COVID-19 with pulmonary infiltrates and oxygen saturation > 94% on room air

receive one of four study drugs (remdesivir, hydroxychloroquine, lopinavir, or interferon-β1a) or standard of care [19, 20]. In the 2021 interim analysis of Solidarity, in which 2750 individuals were assigned to remdesivir, the effect of remdesivir on mortality did not reach statistical significance [19]. The final analysis of Solidarity, published in 2022, included 14,221 patients, of whom 8275 were allocated 1:1 to remdesivir (daily infusion for up to 10 days) or its control (no study drug); inpatient mortality (primary outcome) was 14.5% among patients assigned to remdesivir versus 15.6% for controls (mortality rate ratio, 0.91; 95% CI 0.82–1.02; $P = 0.12$) [20]. Among patients ventilated at baseline, there was no significant difference in mortality for remdesivir versus control. However, patients on LFO or high-flow oxygen (HFO) at baseline, who represented 70% of the study population, did experience a significant mortality benefit with remdesivir versus control (mortality rate ratio, 0.87; 95% CI 0.76–0.99; $P = 0.03$). Additionally, among patients not initially ventilated, remdesivir reduced mortality (rate ratio, 0.86; 95% CI 0.76–0.98; $P = 0.02$) and progression to requiring ventilation (rate ratio, 0.88; 95% CI 0.77–1.00; $P = 0.04$). Overall, findings from Solidarity showed that remdesivir had a meaningful effect on reducing risk of death or progression to mechanical ventilation in hospitalized patients requiring supplemental oxygen but not yet ventilated. Results of the final analysis of Solidarity superseded equivocal findings of the interim report and led to updated WHO guidelines endorsing the use of remdesivir [22].

A clear clinical benefit of remdesivir for outpatient treatment of COVID-19 was shown in PINETREE, a randomized, double-blind, placebo-controlled trial comparing 3-day intravenously administered remdesivir to placebo in nonhospitalized patients aged $\geq$ 12 years with COVID-19, symptom onset $\leq$ 7 days before randomization, and $\geq$ 1 risk factor for progression to severe disease [12]. Remdesivir reduced the risk of hospitalization or death (any cause) by 87% (HR 0.13; 95% CI 0.03–0.59; $P = 0.008$) versus placebo. In a secondary analysis assessing heterogeneity of treatment effect, treatment with remdesivir reduced COVID-19-related hospitalizations independent of stratification by time from symptom onset to randomization and by number of baseline risk factors for severe disease, suggesting a consistent treatment effect in patients with baseline comorbidities [37]. Results of PINETREE led to the expanded FDA approval of remdesivir in January 2022 for use in outpatients with mild-to-moderate COVID-19 at risk of progression to severe COVID-19 [26]. According to NIH guidelines [17], patients hospitalized for reasons other than COVID-19 who test positive for SARS-CoV-2 infection and are at high risk of progression to severe disease may be treated with outpatient regimens; the results of PINETREE indicate a 3-day course of remdesivir should be considered in this clinical setting.

Many studies have underlined the importance of early antiviral treatment for COVID-19, including PINETREE, ACTT-1, and real-world effectiveness studies [11, 12, 14, 38–40]. The early clinical course and immune response to COVID-19 appear to be driven by viral replication, which peaks at or shortly before symptom onset [41–43]. Early antiviral therapy, rather than immunomodulatory therapy, may play a central role in blunting subsequent systemic damage caused by a dysregulated immune response [17, 44]. In accord with these observations, clinical guidelines from the NIH and IDSA suggest that remdesivir has the greatest benefit when administered early in the course of COVID-19, or within approximately 7 to 10 days of symptom onset [17, 18]. However, it is not always possible for patients to identify the exact date of the onset of their symptoms, especially in cases where symptoms are gradual or nonspecific, and therapeutic benefit does not decline stepwise outside this suggested treatment window. Because patient-centric care involves weighing the potential risks and benefits of therapy on an individual basis, there is no justification to deprive a patient of treatment solely on the basis of uncertainties of symptom onset.

Studies suggest that a shorter course of remdesivir in hospitalized patients is warranted in most cases. Goldman et al. reported a randomized, open-label, phase 3 trial (GS-US-540-5773) comparing 5 and 10 days of treatment

with remdesivir in patients aged ≥ 12 years hospitalized with severe COVID-19 not requiring mechanical ventilation at baseline [33]. There was no significant difference in efficacy (mortality, recovery, time to clinical improvement) between 5-day and 10-day courses of remdesivir. At 14 days, numerically lower mortality and shorter time to clinical improvement were seen with the shorter course of remdesivir; however, the group receiving the longer course of remdesivir had more severe disease at baseline and included a higher proportion of men, a group at greater risk of severe COVID-19 [33, 45]. In another randomized, open-label, phase 3 trial of hospitalized patients aged ≥ 12 years with confirmed COVID-19 in the USA (GS-US-540-5774), patients assigned to 5-day remdesivir had significantly higher odds of a better clinical status at day 11 than those assigned to standard care (odds ratio [OR], 1.65; 95% CI 1.09–2.48; $P = 0.02$) [34]. These trial results led to adoption of a 5-day course of remdesivir as the preferred regimen in clinical guidelines [17, 18].

A systematic review and meta-analysis of eight randomized trials ($N = 10{,}751$ patients) found a high probability that remdesivir reduces mortality for nonventilated patients with COVID-19 requiring supplemental oxygen therapy [13]. In a comparison of patients receiving remdesivir to untreated controls, the risk ratio (RR) for mortality was 0.77 (95% CI 0.50–1.19) in patients not requiring supplemental oxygen, 0.89 (95% CI 0.79–0.99) in nonventilated patients requiring supplemental oxygen, and 1.08 (95% CI 0.88–1.31) in patients requiring mechanical ventilation. As part of Solidarity's final analysis and consistent with the study's main findings, a meta-analysis including all major randomized trials to date also showed a mortality benefit with remdesivir versus control in nonventilated patients receiving supplemental oxygen (rate ratio, 0.85; 95% CI 0.75–0.96). A 2023 meta-analysis using individual patient data (allowing standardized outcome and subgroup definitions) and including 99% of all patients in randomized clinical trials involving remdesivir worldwide found that remdesivir significantly reduced mortality in patients hospitalized with COVID-19 with or without supplemental oxygen (adjusted OR [aOR], 0.80; 95% CI 0.70–0.93) and reduced progression to mechanical ventilation (aOR 0.63; 95% CI 0.48–0.83) [46]. Although the findings for patients requiring mechanical ventilation at baseline were inconclusive, the study recommended individualizing treatment approaches to remdesivir use in this population.

Observational and real-world effectiveness studies for remdesivir are summarized in Table 3 [14, 38–40, 47–56] and have generally supported improved rates of survival and clinical improvement [14, 38–40, 47–52, 57–60]. In a retrospective cohort study using US health insurance claims and hospital chargemaster data for 24,856 remdesivir-treated patients and 24,856 propensity score-matched controls, remdesivir was associated with a 17% reduction in inpatient mortality at 28 days among patients hospitalized with COVID-19 compared to propensity score-matched controls (HR 0.83; 95% CI 0.79–0.87) [47]. A study of patients with moderate-to-severe COVID-19 pneumonia in three Spanish hospitals found that remdesivir-treated individuals ($n = 812$) had 37% lower in-hospital mortality compared to propensity score-matched controls ($n = 2703$) not receiving remdesivir (HR 0.63; 95% CI 0.49–0.81; $P < 0.001$) [48]. Similar findings have been observed in multiple large, multicenter, retrospective cohort studies of hospitalized patients in various countries, all showing improved survival in individuals receiving remdesivir compared to those not given remdesivir [39, 52, 58, 60].

Real-world studies have also demonstrated the benefit of early treatment, and large cohort studies have reported a 70% reduction in in-hospital mortality in patients receiving remdesivir within 7 to 10 days of symptom onset versus no remdesivir [38]. Large studies using the PINC AI Healthcare Database, covering approximately 25% of all US hospitalizations from 48 states, have shown improved survival with early remdesivir compared to no remdesivir, including in individuals requiring invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO) [14, 40]. Remdesivir use in patients requiring supplemental oxygen upon admission was assessed in

Table 3 Summary of observational and real-world effectiveness studies for remdesivir in adults

Study	Population	Study period	Patients	Country	Comparison groups	Outcomes
Karolyi et al. (2022) [38]	Aged ≥ 18 years, hospitalized to non-ICU care with COVID-19[a]	June 2020–March 2021	350 (mean age, 64 years; 41% female)	Austria	(1) RDV (n = 175) (2) Non-RDV (n = 175)	RDV reduced in-hospital mortality risk by 74% in patients treated ≤ 7 days from symptom onset and by 82% in female patients
Huang et al. (2022) [39]	Aged ≥ 18 years, hospitalized with COVID-19[a] and discharged alive	May 2020–September 2020 (recruitment)	3508 (median age, 57 years; 45% female; 69% Hispanic)	USA	(1) RDV (n = 1580) (2) Non-RDV (n = 1928)	RDV reduced odds by approximately 50% for composite outcome of all-cause admission or mortality ≤ 14 days after discharge, especially for symptom duration ≤ 10 days
Mozaffari et al. (2022) [40]	Aged ≥ 18 years, hospitalized with COVID-19	August 2020–November 2020	45,542 (55% aged ≥ 65 years; 45% female; 16% Hispanic)	USA	(1) RDV started within ≤ 2 days of admission (n = 28,855) (2) Non-RDV (n = 16,687)	RDV improved 14- and 28-day survival overall and across NSO, LFO, and IMV/ECMO subgroups
Chokkalingam et al. (2022) [47]	Age ≥ 18 years, hospitalized with COVID-19	May 2020–May 2021	49,712 (mean age, 67 years; 48% female; 30% ICU admitted)	USA	(1) RDV (n = 24,856) (2) Non-RDV (n = 24,856)	RDV reduced in-hospital mortality risk by 17%
Arribas López et al. (2023) [48]	Age ≥ 12 years, hospitalized with COVID-19	January 2021–March 2022	3515 (median age, 69 years; 40% female)	Spain	(1) RDV (n = 812) (2) Non-RDV (n = 2703)	RDV reduced in-hospital mortality risk by 37%

Table 3 continued

Study	Population	Study period	Patients	Country	Comparison groups	Outcomes
Finn et al. (2022) [52]	Age ≥ 18 years, hospitalized with COVID-19[a] and discharged alive	April 2020–December 2020	2062 (mean age, 63 years; 46% female; 33% Hispanic)	USA	(1) RDV (n = 742) (2) Non-RDV (n = 1369)	RDV was associated with 19% reduced risk of readmission overall, especially for mild disease
Mozaffari et al. (2023) [14]	Age ≥ 18 years, hospitalized with COVID-19 on supplemental oxygen at baseline	December 2020–April 2022	179,264 (48% aged ≥ 65 years; 47% female; 14% Hispanic)	USA	(1) RDV started within ≤ 2 days of admission (n = 125,806) (2) Non-RDV (n = 53,458)	In patients requiring supplemental oxygen upon admission, RDV reduced 14- and 28-day in-hospital mortality risk by approximately 10–30%
Mozaffari et al. (2023) [53]	Age ≥ 18 years, hospitalized with COVID-19	May 2020–April 2022	440,601 (median age, 63 years; 49% female; 16% Hispanic)	USA	(1) RDV started within ≤ 2 days of admission (n = 248,785) (2) Non-RDV (n = 191,816)	RDV lowered odds of readmission by 27%; this effect was consistent across all dominant variant periods during the study
Gupta et al. (2023) [54]	Age ≥ 18 years, admitted to the ICU with COVID-19	June 2021–February 2022	8044	USA	(1) RDV (n = 4022) (2) Non-RDV (n = 4022)	RDV reduced risk of hospital readmission at 30, 60, and 90 days by approximately 20–40% during Delta and Omicron variant periods
Wiley et al. (2022) [55]	Age ≥ 18 years, hospitalized with COVID-19[a]	March-December 2020	7155 (40% aged ≥ 65 years; 47% female; 25% ICU admitted)	USA	(1) RDV (n = 1832) (2) Non-RDV (n = 5323)	RDV reduced odds of 30-day readmission by approximately 50%

Table 3 continued

Study	Population	Study period	Patients	Country	Comparison groups	Outcomes
Mozaffari et al. (2023) [49]	Age ≥ 18 years with immunocompromising conditions, hospitalized with COVID-19	December 2020–April 2022	30,397 (56% aged ≥ 65 years; 51% female; 19% ICU admitted)	USA	(1) RDV (n = 19,184) (2) Non-RDV (n = 11,213)	Among patients with immunocompromise, RDV reduced 14- and 28-day mortality risk during all variant periods and across all baseline oxygen requirements (NSO, LFO, HFO/NIV, IMV/ECMO)
Lee et al. (2023) [56]	Age ≥ 18 years with immunocompromising conditions, hospitalized with COVID-19	May 2020–November 2022	4664 (mean age, 62 years; 40% ICU care received)	USA	(1) RDV (n = 2332) (2) Non-RDV (n = 2332)	Among patients with immunocompromise, RDV reduced 30- and 60-day risk of hospital readmission by 16%
Mozaffari et al. (2023) [50]	Age ≥ 18 years with cancer, hospitalized with COVID-19	December 2020–April 2022	9874 (80% aged ≥ 65 years; 47% female; 9% Hispanic; 18% ICU admitted)	USA	(1) RDV (n = 4937) (2) Non-RDV (n = 4937)	Among patients with immunocompromise, RDV reduced 14- and 28-day mortality by approximately 30–40%
Rajme-López et al. (2023) [51]	Age ≥ 18 years with immunocompromising conditions, hospitalized with COVID-19[a]	December 2021–April 2022	126 (median age, 49 years; 57% female; 94% immunosuppressed)	Mexico	(1) RDV (n = 54) (2) Non-RDV (n = 72)	Among patients with immunocompromise, RDV reduced odds of composite hospitalization or death by approximately 80%

ECMO extracorporeal membrane oxygenation, *HFO* high-flow oxygen, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *LFO* low-flow oxygen, *NIV* noninvasive ventilation, *NSO* no supplemental oxygen, *RDV* remdesivir

[a]Laboratory-confirmed COVID-19

a comparative effectiveness study of patients treated with remdesivir (67,582 LFO, 34,857 HFO/noninvasive ventilation [NIV], and 4164 IMV/ECMO) propensity score matched (1:1 preferential within-hospital matching with replacement) to patients not given remdesivir between December 2020 and April 2022 [14]. Compared to non-remdesivir treatment, remdesivir initiated $\leq$ 2 days after hospitalization was associated with a significant reduction in in-hospital mortality rates at 14 days by approximately 15–30% across different supplemental oxygen requirements (LFO: adjusted HR [aHR], 0.72; 95% CI 0.66–0.79; HFO/NIV: aHR 0.83; 95% CI 0.77–0.89; IMV/ECMO: aHR 0.73; 95% CI 0.65–0.82; all $P < 0.0001$). Similar mortality reductions were seen at 28 days, and the impact was consistent across all dominant variant periods (pre-Delta, Delta, and Omicron). In another study of 28,855 patients treated with remdesivir $\leq$ 2 days after hospitalization who were propensity score matched to 16,687 non-remdesivir controls, remdesivir improved survival at 14 days (10.6% vs 15.4% mortality for remdesivir and control, respectively; HR 0.76; 95% CI 0.70–0.83) and 28 days (15.4% vs 19.1% mortality; HR 0.89; 95% CI 0.82–0.96) [40]. This mortality benefit was consistent across groups receiving no supplemental oxygen charges, LFO, and IMV/ECMO.

Overall, remdesivir appears to improve survival, and reductions in mortality appear to be consistent across different patient populations and variant periods. Furthermore, results of the PINETREE study support the early use of remdesivir in patients at high risk of progression to severe COVID-19 in outpatient settings and for patients with SARS-CoV-2 infection hospitalized for reasons other than COVID-19, according to NIH guidelines [12, 17]. Notably, new evidence appears to support the benefit of early remdesivir administration in patients with greater COVID-19 severity [48] and irrespective of baseline oxygenation status, including in those with greater supplemental oxygen requirements (HFO/NIV and IMV/ECMO) [14].

TIME ON SUPPLEMENTAL OXYGEN AND LENGTH OF STAY

Studies show that remdesivir reduces supplemental oxygen duration and/or initiation. Among the 913 patients receiving oxygen at enrollment in the ACTT-1 study, patients given remdesivir for 10 days, compared to those given placebo, required supplemental oxygen for fewer days (median, 13 vs 21 days, respectively). Additionally, among the 138 patients not requiring supplemental oxygen at baseline, patients receiving remdesivir had a lower incidence of new oxygen use (36% vs 44%) [11]. Compared to patients not receiving remdesivir, patients given remdesivir and on IMV/ECMO at baseline required IMV/ECMO for fewer days (median, 17 vs 20 days); those not on IMV/ECMO at baseline also had a lower incidence of new use (13% vs 23%). Canadian Treatments for COVID-19 (CATCO), a substudy of Solidarity, was an open-label randomized controlled trial funded by the Canadian Institutes of Health Research; patients were randomized 1:1 (unstratified) to 10-day remdesivir plus standard of care or standard of care alone [35]. Among patients not mechanically ventilated at baseline, incident mechanical ventilation use was lower in the remdesivir group compared to the standard-of-care group (8.0% vs 15.0%; RR 0.53; 95% CI 0.38–0.75). Because patients requiring mechanical ventilation are subject to increased risk of complications, poor outcomes, and prolonged duration of hospitalization, lowering the incidence of mechanical ventilation may ultimately decrease LOS [61].

Some studies of LOS indicate shorter stay with the use of remdesivir. ACTT-1 showed an overall reduction in LOS by 5 days for remdesivir versus placebo (median, 12 vs 17 days), and a retrospective cohort study including all hospitalized patients with confirmed COVID-19 in Hong Kong (N = 10,419) found that patients given remdesivir had shorter LOS than propensity score-matched controls (− 2.6 days; 95% CI − 4.9 to − 0.3; P = 0.029) [11, 59]. Some studies have shown a slightly longer LOS among patients receiving remdesivir compared to those not receiving remdesivir [20, 35, 38, 52, 57, 62];

however, this may be attributable in part to selection bias, whereby patients receiving remdesivir were likely to be more seriously ill than those not given remdesivir [63]. Because longer LOS was also seen in propensity score-matched studies [38, 57], it was likely that patients receiving remdesivir stayed in the hospital longer to complete the 5- or 10-day course of remdesivir treatment [63]. Heterogeneity in methodology, study design, study population, and sample size in these studies also limits generalizability and direct comparisons regarding LOS.

30-DAY READMISSIONS

Large, real-world studies have shown that remdesivir reduces the risk of hospital readmission by approximately 20% to 50% compared to no remdesivir [39, 52–55, 64]. In a large cohort of 440,601 patients hospitalized with a primary diagnosis of COVID-19 and discharged alive in the PINC AI Healthcare Database, remdesivir was associated with significantly lower odds of all-cause 30-day readmission versus no remdesivir (aOR 0.73; 95% CI 0.72–0.75; $P < 0.001$) [53]. The lower odds of readmission for remdesivir-treated individuals were consistent across all variant periods (May 2020–April 2022) and were observed despite a higher supplemental oxygen requirement in the remdesivir group during the index hospitalization. In a study of 8044 patients admitted to intensive care units in US hospitals, remdesivir reduced the 30-, 60-, and 90-day risk of hospital readmission by 20–40% during periods when the Delta and Omicron variants predominated [54]. Individuals treated with remdesivir in a multicenter cohort study in Rhode Island were 19% less likely to be readmitted within 30 days compared to controls (RR 0.81; 95% CI 0.59–1.13); this association was strongest for patients with mild disease (RR 0.31; 95% CI 0.13–0.75) [52]. A study of 3508 patients among 15 medical centers within Kaiser Permanente California found that remdesivir treatment during the index hospitalization was associated with lower odds of the composite endpoint of 14-day all-cause readmission or death (OR 0.46; 95% CI 0.36–0.61), especially for those receiving remdesivir ≤ 10 days from symptom onset [39]. In a retrospective cohort of 463 patients readmitted ≤ 30 days after index hospitalization discharge in eight Atlanta hospitals, Wiley et al. found that patients receiving remdesivir had lower odds of 30-day readmission (OR 0.5; 95% CI 0.4–0.8; $P < 0.001$) compared to patients not receiving remdesivir [55]. Patients receiving both remdesivir and dexamethasone during index hospitalization had lower odds of readmission (OR 0.6; 95% CI 0.4–0.7; $P = 0.002$) compared to dexamethasone alone.

SPECIAL POPULATIONS

Large, real-world observational studies have shown that remdesivir is associated with reduced rates of mortality and hospitalization in immunocompromised populations [49–51, 56]. In a large, retrospective cohort study using the PINC AI Healthcare Database and including patients with immunocompromising conditions in 819 US hospitals from December 2020 to April 2022, 14,169 patients hospitalized with a primary diagnosis of COVID-19 and administered remdesivir ≤ 2 days from admission were propensity score matched to 5341 individuals not given remdesivir [49]. Remdesivir was associated with significantly lower overall mortality risk at 14 days (aHR 0.70; 95% CI 0.62–0.78; $P < 0.001$) and 28 days (aHR 0.75; 95% CI 0.68–0.83; $P < 0.001$). Despite longitudinal changes in patient characteristics and outcomes across the study period, this remdesivir-associated mortality reduction was consistent across all baseline supplemental oxygen requirements (including no supplementary oxygen, LFO, HFO/NIV, and IMV/ECMO) and variant periods (pre-Delta, Delta, and Omicron). In a study of 4664 individuals with immunocompromising conditions who were hospitalized with COVID-19 from May 2020 to November 2022 in the US HealthVerity database, those treated with remdesivir had a 16% reduced risk of hospital readmission at 30 and 60 days relative to untreated controls [56]. A study of patients with cancer hospitalized for COVID-19 using the

PINC AI Healthcare Database from December 2020 to April 2022, including 4937 patients who were treated with remdesivir and propensity score matched to 2088 non-remdesivir patients, found that remdesivir significantly reduced mortality by 41% and 33% (both $P < 0.001$) at 14 and 28 days, respectively, relative to non-remdesivir controls, with similar reductions observed during all variant periods [50].

Remdesivir use in nonhospitalized patients was assessed in a prospective cohort study of 126 patients with mild-to-moderate COVID-19 at high risk of progression to severe disease, including a majority (94%) who were immunosuppressed [51]. Early outpatient treatment with remdesivir (within 7 days of symptom onset) compared to no remdesivir treatment was independently associated with 80% reduced odds of hospitalization or death (aHR 0.16; 95% CI 0.06–0.44; $P < 0.01$).

Use of remdesivir in individuals with moderate-to-severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) was assessed in REDPINE, a randomized, double-blind, placebo-controlled phase 3 trial including individuals with acute kidney injury, chronic kidney disease, or end-stage kidney disease who were hospitalized with a primary diagnosis of COVID-19 pneumonia [36]. Safety outcomes were similar for a 5-day course of remdesivir ($n = 163$) compared to placebo ($n = 80$), suggesting that no dose adjustment is needed with this regimen in patients with varying degrees of renal dysfunction.

Taken together, multiple large, nationally representative real-world studies among individuals with immunocompromising conditions show that early administration of remdesivir is associated with improved survival in this vulnerable population irrespective of supplementary oxygen requirements and dominant SARS-CoV-2 variants. Furthermore, the American Society of Transplantation preferentially recommends remdesivir as first-line therapy to prevent disease progression in nonhospitalized transplant patients, in part because nirmatrelvir/ritonavir, an oral antiviral approved for treatment of COVID-19, can interact with immunosuppressive calcineurin inhibitors or mechanistic target of rapamycin (mTOR) inhibitors [17, 65, 66]. Some case reports of immunocompromised patients with prolonged or persistent COVID-19 have shown treatment response or temporary suppression with prolonged or repeated courses of remdesivir, indicating that longer treatment duration may be needed in some similar situations [67–69]. Furthermore, immunocompromised patients experience high rates of post-COVID conditions, and the use of remdesivir to prevent this long-term syndrome is an area of active research [70].

CONCLUSIONS

Remdesivir, compared to standard of care, appears to improve survival overall. In certain subpopulations, remdesivir also increases rate of recovery and reduces readmission rate and time to clinical improvement. Utilizing larger data sets, real-world studies are generating further evidence supporting a reduction in mortality associated with remdesivir in diverse, representative populations and subgroups. Notably, accumulating data are beginning to suggest a clinical benefit associated with remdesivir use irrespective of baseline oxygen status or circulating SARS-CoV-2 variants, and also in high-risk or immunocompromised populations. The impact of remdesivir on post-COVID conditions is an area of considerable interest and active research. Alongside these new data, clinical guidelines continue to evolve and expand recommendations regarding the use of remdesivir across the breadth of COVID-19 severity. Overall, the literature to date supports the early use of remdesivir in a broad range of hospitalized and nonhospitalized individuals experiencing COVID-19 at various degrees of severity.

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Declarations

Conflict of Interest. Patrick O. Godwin reports consulting fees for the development and review of educational materials; payments for lectures and participation in a speaker bureau; and travel-related expenses for lectures, speaker training, and advisory boards from Gilead Sciences, Inc. Bryan Polsonetti, Michael F. Caron, and Thomas F. Oppelt are employees and stockholders of Gilead Sciences, Inc.

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