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# EFFECT OF REMDESIVIR USE ON PATIENTS' VIRAL LOAD WITH COVID-19: A META-ANALYSIS OF RANDOMISED CLINICAL TRIALS

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## ABSTRACT

**Objectives**: To assess the role of remdesivir in the viral load of patients with COVID-19, we conducted a systematic review and meta-analysis. **Methods**: PubMed and Cochrane Library databases were searched until December 20, 2021. Randomized controlled trials that reported an association between remdesivir use and viral load, clinical recovery, mortality, and serious adverse events were included. **Results**: Among the 2,028 studies found, seven meet the inclusion criteria, totalling 8,429 patients. In the remdesivir group, there was no difference in the viral load on 5-day of therapy or in the 28-day mortality outcome. However, it was observed a decrease in time to clinical recovery (RR = 1.19, 95% CI 1.07-1.31), and when treatment occurs for up to 10 days, the RR is 1.34 (95% CI 1.13 -1.55). The risk of serious adverse events was lower in the remdesivir group than the control group. **Conclusion**: This study suggests that remdesivir use did not reduce viral load. Studies with early initiation of the therapy are needed to confirm this finding.

**KEYWORDS**: Antiviral Agents, COVID-19, Meta-analysis, Remdesivir, SARS-CoV-2, Systematic Review.

## INTRODUCTION

The World Health Organization (WHO) has declared the COVID-19 pandemic on March 11, 2020.[1] Since then, there have been more than 270 million cases, with 5.31 million deaths from COVID-19 worldwide until December 15, 2021.[2]

This number could be even higher if it weren't for expanding vaccination campaigns. In Europe alone, it is estimated that approximately 470,000 lives have been saved among those aged 60 years and over due to vaccination. However, despite this massive contribution of vaccines, drugs still play a central role in containing deaths from COVID-19.[3]

Remdesivir (Veklury®, Gilead Sciences), a broad-spectrum antiviral that was initially developed to treat patients infected with the Ebola virus, emerged as a candidate, and despite not showing benefit in mortality, it was approved by Food and Drug Administration (FDA) after studies showed a reduction in clinical recovery time and adverse events.[4–9]

Although *in vitro* studies have shown that remdesivir was effective against the prominent representatives of the coronaviridae family: SARS-CoV-1, MERS-CoV, and SARS-CoV-2, and studies showing some clinical benefit in COVID-19, viral clearance has been little studied.[10–12]

In such a scenario, we proposed to conduct a systematic review and meta-analysis to assess the effect of remdesivir use on viral load, mortality, clinical recovery, and serious adverse events in patients with COVID-19.

## METHODS

This systematic review was conducted following the Preferred Items guidelines for Reporting for Systematic Reviews and Meta-Analysis (PRISMA). This study has not been registered.

Search for published studies was conducted in PubMed, Cochrane Library, and MedRxiv prepress server due to the urgency of publications related to COVID-19. We have included studies published until December 20, 2021. The following keywords were used as search terms: (covid-19 OR "severe acute respiratory syndrome coronavirus 2" OR coronavirus OR betacoronavirus) AND (remdesivir OR "remdesivir triphosphate" OR GS-441524). The references for all selected articles were also retrieved.

***Studies Selection and Inclusion Criteria***

After searching databases and removing duplicates, two independent authors screened the titles/abstracts. Disagreements were solved through discussion among all authors, followed by screening. Randomised controlled trials were included considering the following PICO criteria: (1) Adult patients with COVID-19; (2) patients using remdesivir; (3) patients who did not use remdesivir as the comparator, and (4) randomised clinical trials that reported the outcomes: viral load, clinical recovery, serious adverse events, or mortality.

We considered as serious adverse events multiple organ dysfunction syndromes, respiratory failure or acute respiratory distress syndrome, cardiopulmonary failure, pulmonary embolism, pneumothorax, acute kidney injury, renal failure, cardiac arrest, atrial fibrillation, acute coronary syndrome, tachycardia, septic shock, hypotension, and shock.

***Data Extraction***

Two authors did data extraction separately according to a data collection form. The information extracted includes authors, year of publication, study design, country of origin, population characteristics (age and sample size), type of treatment, disease severity, duration of follow-up, and measurement of effects for the researched outcomes: estimated differences in viral load decrease; odds ratio (OR), relative risk (RR) or hazard ratio (HR) with 95% confidence intervals (CI) for the other outcomes. Inclusion was not restricted by study size.

***Risk of Bias***

Two authors independently assessed the quality of studies according to the Cochrane guidelines.[13] The following five domains were assessed: (1) bias arising from the randomisation process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; (5) bias in the selection of the reported result. Disagreements were solved through discussion with a third author.

***Statistical Analysis and Assessment of Heterogeneity***

Viral load outcome was analysed with the standardised mean difference (SMD) with a 95% confidence interval (CI), according to Higgins et al.[14] Mortality, clinical recovery, and adverse events were included in the meta-analysis reported RR or HR. For studies that did not report these effects, the RR calculation was based on the Cochrane Handbook for Systematic Reviews.[13] Pooled RR and 95% confidence interval (CI) were calculated using a fixed or random-effects model according to the studies' homogeneity.

The Cochran Q test and the $I^2$ statistic evaluated the statistical significance and degree of heterogeneity between the studies, respectively. A result of $p < 0.05$ for the Q test represents statistical significance. The statistic $I^2$ was used to address the heterogeneity within the studies. The interpretation of its value was based on Cochrane Handbook for Systematic Reviews of 28 Interventions, as follows: 0% to 40%: might not be significant; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity.[15] The Egger test examined the publication bias to detect small-study effects. All analysis was performed with Stata/SE v.14.1 software (StataCorp, College Station, 20 TX, USA).

## RESULTS

***Study Selection and Characteristics of Included Studies***

Two thousand and twenty-eight (2,028) studies were identified in the initial search. Of these, seventeen were duplicated, and two thousand and four were removed because of exclusion criteria: observational studies, non-therapeutic, without comparator group and non-randomised studies. Seven studies were included in the meta-analysis (Figure 1), comprising 8,429 patients. Two studies are double-blind, randomised, placebo-controlled trials.[8,16] and five are randomised, open-label trials.[12,17–19] Three studies assessed the viral load outcome[16,18,19], three assessed clinical recovery.[8,16,19], five assessed mortality.[8,16,17,19,20], and four assessed the serious adverse events.[8,12,16,19] The basic characteristics of the included studies are shown in Table 1.

***Effect of remdesivir therapy on viral load***

Viral load data were extracted from three studies.[16,18,19] The viral load data were obtained from analyses performed using upper (nasopharyngeal or oropharyngeal swabs) respiratory tract specimens between days 3 to 5 after randomisation. These data are shown in Figure 2. The analysis showed no difference in viral load in the remdesivir group compared to the control group (SMD=-0.09, 95%CI -0.34; 0.15, *P*=0.131).

***Effect of Remdesivir Therapy on Clinical Recovery***

The data was extracted from three studies[8,16,19], and the outcome was measured as a decrease in clinical recovery time, which was observed a better result in the treatment group (RR=1.19, 95%CI 1.07-1.31, *P*<0.001). In subgroup analysis, patients who received remdesivir within 10 days of the onset of symptoms decreased clinical recovery time compared to patients who received remdesivir after 10 days (RR=1.34, 95%CI 1.13-1.55; RR=1.18, 95%CI 0.91-1.44, respectively). These data are shown in Figure 3.

***Effect of Remdesivir Therapy on Mortality***

For 28-day mortality outcome, data were extracted from 5 studies [8,16,17,19,20] that showed no differences between patients treated with remdesivir and the control group (RR = 0.90, 95% CI 0.78-1.03). This data is shown in Figure 4.

***Effect of Remdesivir Therapy on Serious Adverse Events***

The data were extracted from 4 studies.[8,12,16,19] Spinner et al.[12] compared two treatment groups (5 and 10 days of treatment with remdesivir) with the control group, treated with standard care. The analysis showed a decreased risk of serious adverse events in the remdesivir treatment group (RR = 0.79, 95% CI 0.59-0.98, *P*<0.001, Figure 5).

A sensitivity analysis was performed for serious adverse events outcomes omitting each study. The omission of Ader et al. removed heterogeneity and did not change the effect estimate (RR = 0.73, 95% CI 0.61-0.86). However, the withdrawal of Beigel et al., Spinner et. al., and Wang et al. indicated that the omission of each of the studies led to changes in effect estimates, indicating weak evidence (Table 2).

Table 3 describes the serious adverse events extracted from the studies Wang et al.[16] and Beigel et al.[8] In the remdesivir group (n = 687), 159 serious adverse events were described: respiratory failure or acute respiratory distress syndrome (62 = 9.02%), acute respiratory failure (8 = 1.16%), respiratory distress (6 = 0.87%), pneumothorax (5 = 0.72%), pulmonary embolism (6 = 0.87%), pneumonia aspiration (4 = 0.58%), lung abscess (0), bronchits (0), hypoxia (4 = 0.58%), cardiopulmonar failure (8 = 1.16%), cardiac arrest (11 = 1.60%), acute coronary syndrome (0), atrial fibrilation (5 = 0.72%), tachycardia (0), hypotension (4 = 0.58%), deep vein thrombosis (1 = 0.14%), increased D-dimer (0), thrombocytopenia (1 = 0.14%), renal failure (2 = 0.29%), acute kidney injury (8 = 1.16%), decreased glomerular filtration rate (GFR) (5 = 0.72%), haemorrhage of lower digestive tract (1 = 0.14%), illeus (0), diabetic ketoacidosis (0), septic shock (9 = 1.31%), shock (5 = 0.72%), sepsis (0), multiple organ dysfunction syndrome (6 = 0.87%).

Otherwise, in the placebo group (n = 594), 183 serious adverse events were found: respiratory failure or acute respiratory distress syndrome (77 = 12.96%), acute respiratory failure (14 = 2.35%), respiratory distress (11 = 1.85%), pneumothorax (5 = 0.84%), pulmonary embolism (5 = 0.84%), pneumonia aspiration (2 = 0.33%), lung abscess (1 = 0.16%), bronchits (1 = 0.16%), hypoxia (4 = 0.67%), cardiopulmnonary failure (7 = 1.17%), cardiac arrest (7 = 1.17%), acute coronary syndrome (1 = 0.16%), atrial fibrilation (1 = 0.16%), tachycardia (1 = 0.16%), hypotension (7 = 1.17%), deep vein thrombosis (1 = 0.16%), increased D-dimer (1 = 0.16%), thrombocytopenia (0), renal failure (5 = 0.84%), acute kidney injury (12 = 2.02%), decreased GFR (2 = 0.33%), haemorrhage of lower digestive tract (0), illeus (1 = 0.16%), diabetic ketoacidosis (1 = 0.16%), septic schock (16 = 2.69%), shock (4 = 0.67%), sepsis (1 = 0.16%), multiple organ dysfunction syndrome (5 = 0.84%).

***Quality assessment of selected studies for meta-analysis and publication bias***

The quality assessments of the studies included in the meta-analysis are shown in Figure 6. Among the studies selected, three trials[8,16,19] were considered as a low risk of bias, three[12,17,18] as some concerns and one[20] as high risk of bias. The estimated bias coefficient was from -0.151 to 4.028, giving a *P*-value > 0.05 for all analyses. Therefore, the tests provide weak evidence for the presence of publication bias.

Sensitivity analyses were not performed when less than four studies were involved in the analysis, or there was low heterogeneity.

**Table 1. Characteristics of studies selected.**

| Author | Year | Country | Study Design | Drugs | Population | Outcomes | Sample size | Age | Treatment group | Control group | Follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ader et al (DisCoVeRy) | 2021 | France, Belgium, Austria, Portugal, and Luxembourg | Randomized, open-label trial | Remdesivir | Hospitalized patients (aged ≥ 18 years) with confirmed covid-19 | Clinical recovery; serious adverse events; viral load; mortality. | 832 | Remdesivir group* 63 (55–73)<br>Control group* 64 (54–72) | 414 | 418 | 29 days |
| Beigel et al. | 2020 | United States, Europe, Asia, and Mexico. | Randomized, double-blind, placebo-controlled trial | Remdesivir | Hospitalized patients (aged ≥ 18 years) with confirmed covid-19 | Clinical recovery; serious adverse events; mortality. | 1062 | Remdesivir group** 58.6±14.6<br>Control group** 59.2±15.4 | 541 | 521 | 28 days |
| Barratt-Due et al (NOR-SOLIDARITY) | 2021 | Norway | Randomized, open-label trial | Remdesivir, HCQ | Hospitalized patients (aged ≥ 18 years) with confirmed covid-19 | Viral load | 181 | Remdesivir group** 59.7±16.5<br>Control group** 58.1±15.7 | 42 | 57 | 15 days |
| Mahajan et al | 2021 | India | Randomized, open-label trial | Remdesivir | Hospitalized patients (aged ≥ 40 years) with moderate to severe COVID- 19 | Death | 70 | Remdesivir group** 58.1±12.1<br>Control group** 57.4±14.1 | 34 | 36 | 12 days |
| Pan et al. (SOLIDARITY) | 2020 | All continentes | Randomized, open-label trial | Remdesivir, HCQ, lopinavir, and interferon | Hospitalized patients (aged ≥ 18 years) with confirmed covid-19 | Mortality. | 5451 | Remdesivir group*** 961 (<50 years), 1282 (50-69 years), and 500 (≥70 years)<br>Control group*** 952 (<50 years), 1287 (50-69 years), and 469 (≥70 years) | 2743 | 2708 | 28 days |
| Spinner et al. | 2020 | United States, Europe, and Asia. | Randomized, open-label trial | Remdesivir | Hospitalized patients (aged ≥ 12 years) with confirmed COVID-19 | Serious adverse events. | 596 | 10-day course of remdesivir* 56 (45-66)<br>5-day course of remdesivir* 58 (48-66)<br>Standard care* 57 (45-66) | 10-day course of remdesivir = 197<br>5-day course of remdesivir = 199 | 200 | 28 days |
| Wang Y et al. | 2020 | China | Randomized, double-blind, placebo-controlled trial | Remdesivir | Hospitalized patients (aged ≥ 18 years) with confirmed COVID-19 and pneumonia confirmed by chest imaging | viral load, clinical recovery; serious adverse events; mortality; viral load. | 237 | Remdesivir group* 66 (57-73)<br>Control group* 64 (53-70) | 158 | 79 | 28 days |

HCQ: Hydroxychloroquine.
* Data represented as median (IQR). **Data represented as mean ±SD. *** Data represented as number of patients.

**Table 2. Sensitive analysis for the results of the serious events adverse.**

| Study omitted | RR | 95% CI | $I^2$ | *P** |
|---|---|---|---|---|
| Ader et al (DisCoVeRy) | 0.73 | 0.61-0.86 | 0.0% | 0.623 |
| Beigel et al | 0.76 | 0.47-1.06 | 64.0% | 0.039 |
| Spinner et al (5 days) | 0.83 | 0.63-1.03 | 57.3% | 0.071 |
| Spinner et al (10 days) | 0.81 | 0.60-1.03 | 61.8% | 0.049 |
| Wang et al | 0.80 | 0.56-1.03 | 64.9% | 0.036 |

* Value for heterogeneity among studies assessed with Cochran's Q test.

**Table 3: Serious adverse events of the studies: Beigel et al. and Wang et al.**

| Remdesivir group (n = 687) | n (%) | Control group (n = 594) | n (%) |
|---|---|---|---|
| Respiratory failure or acute respiratory distress syndrome | 62 (9.02%) | Respiratory failure or acute respiratory distress syndrome | 77 (12.96%) |
| Cardiac arrest | 11 (1.60%) | Septic shock | 16 (2.69%) |
| Septic shock | 9 (1.31%) | Acute respiratory failure | 14 (2.35%) |
| Acute respiratory failure | 8 (1.16%) | Acute kidney injury | 12 (2.02%) |
| Cardiopulmonary failure | 8 (1.16%) | Respiratory distress | 11 (1.85%) |
| Acute kidney injury | 8 (1.16%) | Cardiopulmonary failure | 7 (1.17%) |
| Respiratory distress | 6 (0.87%) | Cardiac arrest | 7 (1.17%) |
| Pulmonary embolism | 6 (0.87%) | Hypotension | 7 (1.17%) |
| Multiple organ dysfunction syndrome | 6 (0.87%) | Pneumothorax | 5 (0.84%) |
| Pneumothorax | 5 (0.72%) | Pulmonary embolism | 5 (0.84%) |
| Atrial fibrillation | 5 (0.72%) | Renal failure | 5 (0.84%) |
| Decreased glomerular filtration rate | 5 (0.72%) | Multiple organ dysfunction syndrome | 5 (0.84%) |
| Shock | 5 (0.72%) | Hypoxia | 4 (0.67%) |
| Aspiration pneumonia | 4 (0.58%) | Shock | 4 (0.67%) |
| Hypoxia | 4 (0.58%) | Aspiration pneumonia | 2 (0.33%) |
| Hypotension | 4 (0.58%) | Decreased glomerular filtration rate | 2 (0.33%) |
| Renal failure | 2 (0.29%) | Lung abscess | 1 (0.16%) |
| Deep vein thrombosis | 1 ( 0.14%) | Bronchitis | 1 (0.16%) |
| Thrombocytopenia | 1 (0.14%) | Acute coronary syndrome | 1 (0.16%) |
| Lower gastrointestinal bleeding | 1 (0.14%) | Atrial fibrillation | 1 (0.16%) |
| Lung abscess | 0 | Tachycardia | 1 (0.16%) |
| Bronchitis | 0 | Deep vein thrombosis | 1 (0.16%) |
| Acute coronary syndrome | 0 | Increased D-dimer | 1 (0.16%) |
| Tachycardia | 0 | Ileus | 1 (0.16%) |
| Increased D-dimer | 0 | Diabetic ketoacidosis | 1 (0.16%) |
| Ileus | 0 | Sepsis | 1 (0.16%) |
| Diabetic ketoacidosis | 0 | Thrombocytopenia | 0 |
| Sepsis | 0 | Lower gastrointestinal bleeding | 0 |

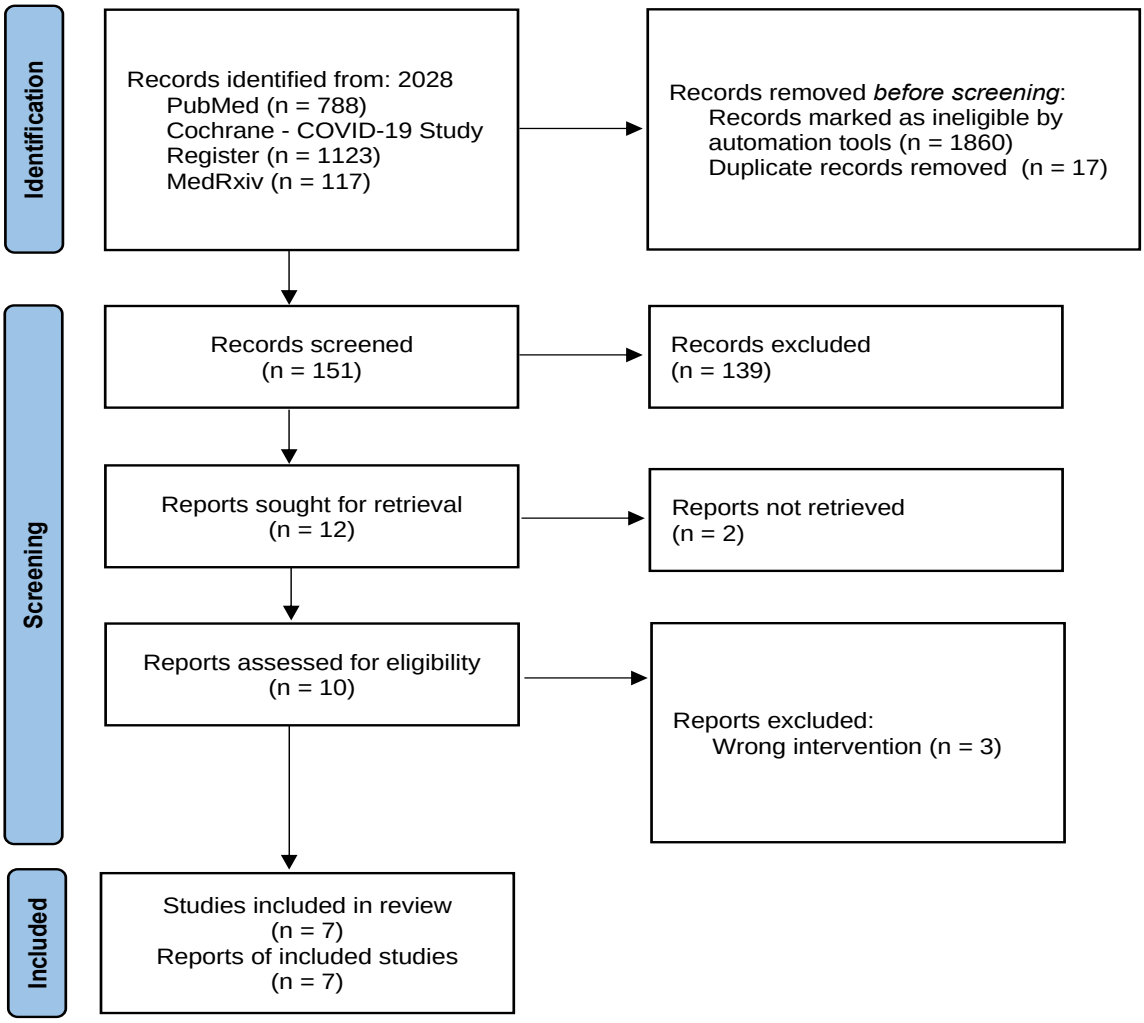


**Figure 1: Flow chart of study selection.**

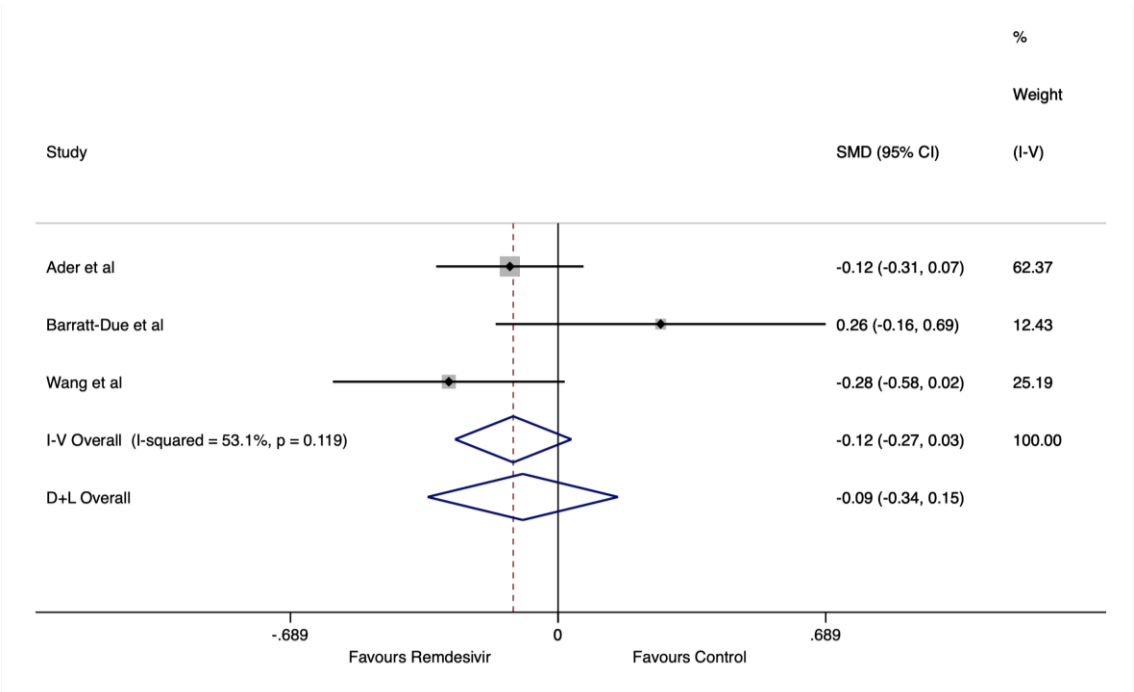


**Figure 2: Effect of remdesivir therapy on the viral load at day 5 after randomisation.**

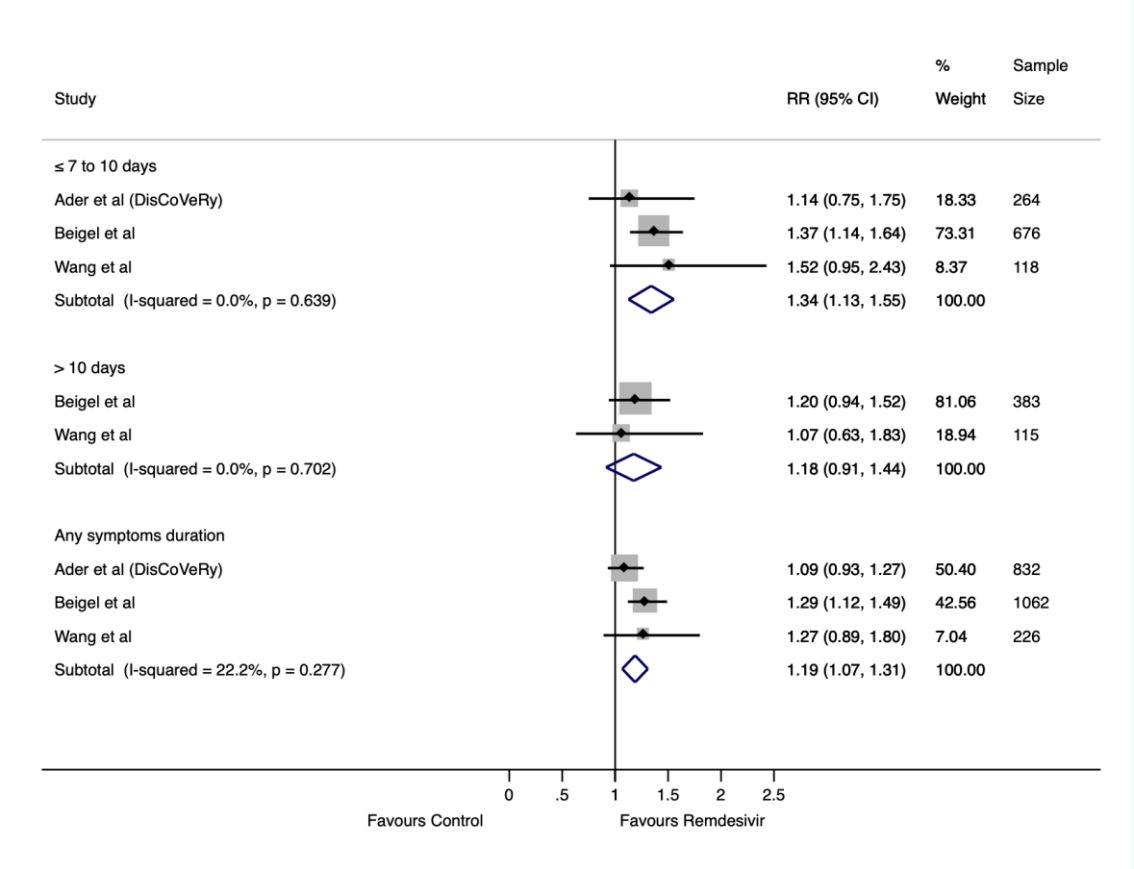


**Figure 3: Effect of remdesivir therapy on clinical recovery for days of symptoms when randomisation is performed.**

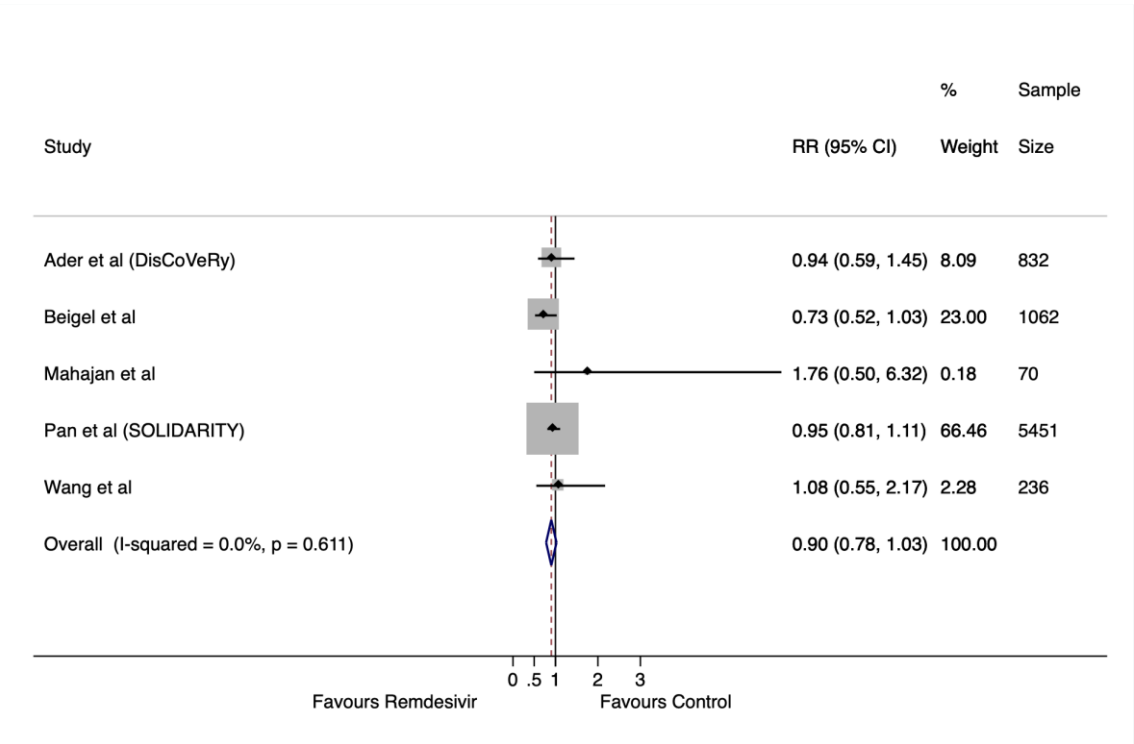


**Figure 4: Effect of remdesivir therapy on 28-days mortality.**

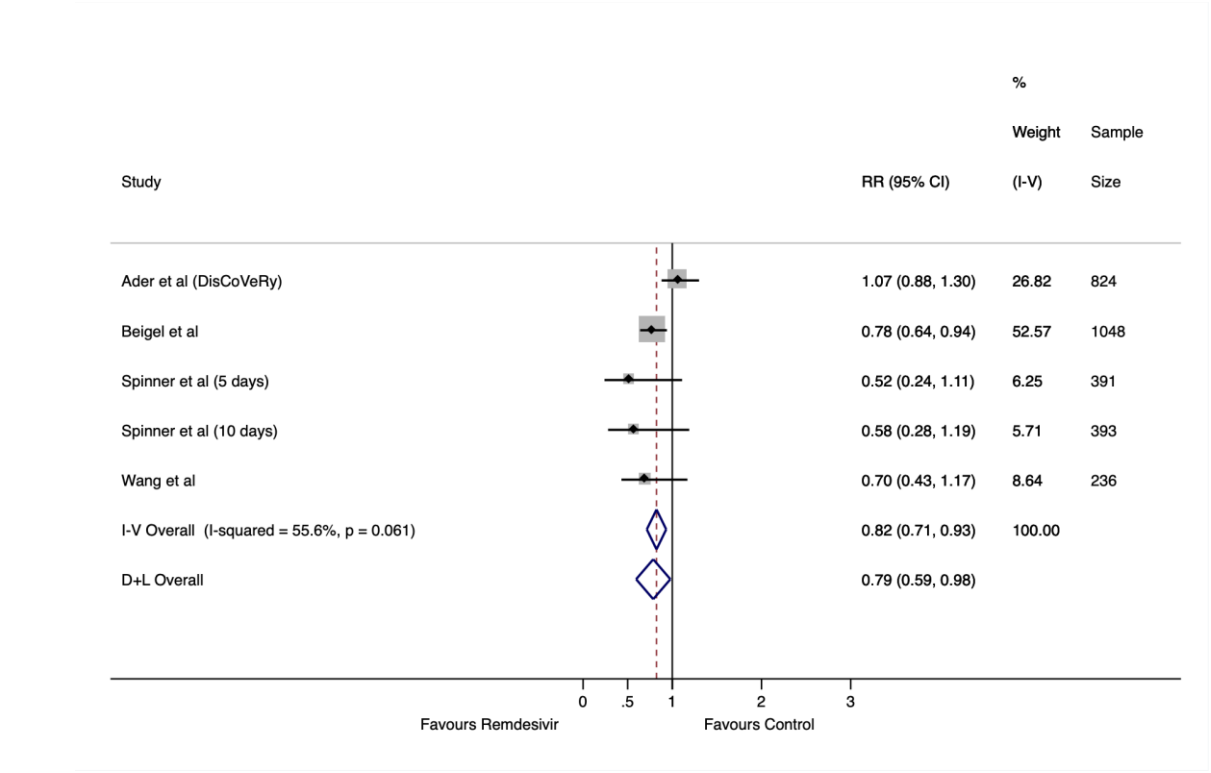


**Figure 5: Effect of remdesivir therapy on serious adverse events. Spinner et al. with two treatment groups (5-day and 10-day regiment).**

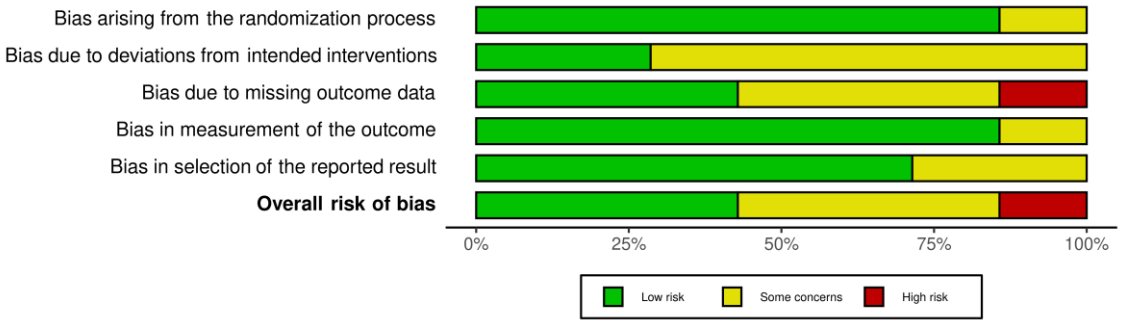


**Figure 6: Quality assessment of the included studies in the meta-analyses.**

## DISCUSSION

This is the first meta-analysis involving viral load in patients with COVID-19 treated with remdesivir and the systematic review of randomised clinical trials addressing remdesivir therapy with the largest number of COVID-19 patients involved.

This study suggests that remdesivir use does not decrease viral load in patients with COVID-19. However, the use of remdesivir can reduce the clinical recovery time of patients hospitalised with COVID-19 compared to the control group if its use starts within 10 days after the onset of symptoms. Besides, patients undergoing treatment with remdesivir had fewer serious adverse events than patients in the control group. However, despite these clinical benefits, remdesivir was not associated with a lower mortality rate than the control group. These results are supported by other studies showing clinical benefits from remdesivir use in COVID-19, albeit with some uncertainty.[7,21,22]

The reasons why the time to clinical recovery was shorter among patients who received remdesivir cannot be fully explained. However, it is likely that as well as other antivirals, remdesivir can improve the prognosis of patients before the infection progresses due to intense viral replication.[23,24]

The presence of clinical benefits, even in the absence of a reduction in viral load, raises some doubts. It is noteworthy that an initial phase of intense viral replication progresses to respiratory failure at days 8–9 in severe infections due to the host inflammatory response.[25] Although severe acute respiratory syndrome coronavirus 2 is still detectable during the hyperinflammatory phase, viral concentrations are

substantially lower in this phase than in the first week of illness.[26]

Additionally, it has been shown that viral load appears to naturally decline after the end of the first week of COVID-19 symptom onset.[27] Despite detecting the virus for weeks, successfully cultivating SARS-CoV-2 occurs until the eighth day of infection, indicating that many patients involved in the trials no longer had the replicating virus but residual viral "debris".[28,29]

Among the studies selected in this systematic review, Beigel et al. divided the patients into two groups according to the duration of symptoms (≤10 days or >10 days) and found a benefit in clinical recovery but did not perform a mortality analysis with this stratification, nor did it assess the viral load. Wang et al. recruited hospitalised COVID-19 patients with up to 12 days of symptoms. Spinner et al. randomised patients into three groups (10-day remdesivir, 5-day remdesivir, and standard care) and showed a median duration of symptoms before the first dose of remdesivir was 8 (IQR 5-11). Ader et al. informed that the median days from symptoms onset to random assignment was 9 (IQR 7-12). While the mean symptom duration before admission was 8 (SD=4.9) for Barrat-Due et al., Mahajan et al. and Pan et al. do not clarify the mean duration of symptoms of the recruited patients.

Furthermore, Wang et al. performed viral load analysis stratifying the patients by symptoms onset. The mean difference in viral load between days 1 and 5 of randomisation in the group receiving remdesivir from ≤10 symptoms onset was -2.38 $\log_{10}$ copies per mL versus -1.62 $\log_{10}$ copies per mL for the >10 symptoms onset group.[16]

Serious adverse events were lower in the remdesivir group than the control group, resulting in a better prognosis. Nevertheless, some of these events were more common in one group than others. Respiratory failure, acute respiratory failure, respiratory distress, acute respiratory distress syndrome, renal failure, acute kidney injury, hypotension, and septic shock were common in the control group. On the other hand, pneumonia aspiration, cardiac arrest, atrial fibrillation, and decreased GFR were more common in the remdesivir group. Other serious adverse events were similar in both groups.

Nonetheless, as the data regarding the remdesivir safety profile are still limited, it is impossible to distinguish with certainty which of these events are complications of COVID-19 and which are due to remdesivir. For example, a case of hypotension was associated with the use of remdesivir in a clinical trial of experimental therapies against Ebola[30], and acute kidney injury, septic shock, hypotension, and multiple organ dysfunction syndromes were the most common serious adverse events reported by Grein et al.[31] in patients who received remdesivir. However, all these events occurred in a reduced or equal proportion among patients who received remdesivir than those who did not. Acute kidney injury was the second most common severe adverse event in the placebo group of a clinical trial conducted by Cao et al.[32], suggesting that it must be a complication of COVID-19. At the same time, hypotension, septic shock, and multiple organ dysfunction syndromes were not reported in the control or placebo group.

Also, as it is a global public health issue, it is necessary to consider whether remdesivir has an adequate cost-benefit to adopt its use on a large scale. There is no simple way to make such an assessment, but an initial way could be comparing whether the reduction in hospitalisation costs resulting from a shorter recovery time is sufficient to pay for the treatment with the antiviral. For the scenario described in this meta-analysis, where remdesivir cannot decrease mortality, its maximum price should be $ 310, a value well below the $ 2,340 set by Gilead Sciences Inc. [33,34] Therefore, there would be no cost-benefit in using remdesivir. However, this relationship changes if it is shown that it is capable of decreasing mortality.

Finally, this study noted that despite reducing the time to clinical recovery and the number of serious adverse events, remdesivir was not superior to the control group of reduced mortality and viral load. However, this divergence of results may have been caused by the prolonged duration of symptoms in the recruited patients, which is a fundamental factor in analysing an antiviral.

Some limitations of this study were the small number of randomised trials on the use of remdesivir, five studies performed without blinding, and different and long duration of symptoms before the first dose of remdesivir. This study informs physicians and patients regarding the efficiency of remdesivir in treating COVID-19. Despite the few selected clinical trials, the studies included comprise 8,429 patients with COVID-19.

## CONCLUSION

This systematic review suggests that remdesivir therapy in patients with COVID-19 does not reduce viral load or mortality. Although it reduces serious adverse events and clinical recovery, these results need to be interpreted with caution. Randomised clinical trials with early initiation of the therapy are required to confirm the effects of remdesivir in COVID-19 patients.

## REFERENCES

1. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 18 March 2020 [Internet]. 2020 [cited 2020 Nov 6]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---18-march-2020.
2. World Health Organization. WHO Coronavirus

Disease (COVID-19) Dashboard With Vaccination Data [Internet]. World Heal Organ. 2021 [cited 2021 Aug 20].; 1–5.
3. Meslé MM, Brown J, Mook P, Hagan J, Pastore R, Bundle N, et al. Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021. Eurosurveillance, 2021 Nov; 26(47): 2101021.
4. Olivero J, Fa JE, Farfán MÁ, Márquez AL, Real R, Juste FJ, et al. Human activities link fruit bat presence to Ebola virus disease outbreaks. Mamm Rev, 2020 Jan; 50(1): 1–10.
5. Prasad M, Elavarasi A, Madan K, Nischal N, Soneja M, Seth T, et al. Efficacy and safety of antivirals for Covid-19: A systematic review and meta-analysis. Natl Med J India, 2020 Jul; 33(4): 222–31.
6. FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment | FDA [Internet]. US Food Drug Adm. 2020 [cited 2020 Nov 10]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment
7. Al-Abdouh A, Bizanti A, Barbarawi M, Jabri A, Kumar A, Fashanu OE, et al. Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. Contemp Clin Trials. 2021 Feb;101. DOI: 10.1016/j.cct.2021.106272
8. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 DOI: 10.1056/nejmoa2007764
9. Pan H, Peto R, Henao-Restrepo A, Preziosi M, Sathi-yamoorthy V, Abdool Karim Q, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med, 2021; 384(6): 497–511.
10. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med, 2017; 9(396). DOI: 10.1126/scitranslmed.aal3653.
11. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res, 2020 Mar; 30(3): 269–71.
12. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. JAMA - J Am Med Assoc, 2020; 324(11): 1048–57.
13. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial | Cochrane Training [Internet]. Cochrane. 2019 [cited 2020 Jun 9]. Available from: https://training.cochrane.org/handbook/current/chapter-08.
14. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect | Cochrane Training [Internet]. Cochrane. 2019 [cited 2020 Jun 9]. Available from: https://training.cochrane.org/handbook/current/chapter-06.
15. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane database Syst Rev, 2019; 10: ED000142.
16. Wang Y, Zhang D, Du G. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2020; 395(10236): 1569–78.
17. Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv, 2020; (October 15): 2020.10.15.20209817.
18. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, Kåsine T, Lund-Johansen F, Hoel H, et al. Evaluation of the effects of remdesivir and hydroxychloroquine on viral clearance in covid-19: A randomized trial. Ann Intern Med, 2021; 174(9): 1261–9.
19. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis, 2021; 19(21): 1–13.
20. Mahajan L, Singh AP, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian J Anaesth, 2021 Mar; 65(13): S41–6.
21. Verdugo-Paiva F, Acuña MP, Solá I, Rada G. Remdesivir for the treatment of COVID-19: a living systematic review. Medwave, 2020 Dec; 20(11): e8080.
22. Enoki Y, Igarashi Y, Watabe Y, Honma K, Suzuki Y, Hayashi Y, et al. Remdesivir for the treatment of coronavirus COVID-19: A meta-analysis of randomised controlled trials. J Glob Antimicrob Resist, 2021; 24: 81–2.
23. Lee N, Chan PKS, Kin WC, Lui G, Wong B, Cockram CS, et al. Factors associated with early hospital discharge of adult influenza patients. Antivir Ther, 2007; 12(4): 501–8.
24. Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Aghayev F, et al. Effectiveness of antiviral treatment in human influenza A(H5N1) infections: Analysis of a global patient registry. J Infect Dis, 2010; 202(8): 1154–60.
25. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol, 2020; 20(6): 363–74.

26. Weiss A, Jellingsø M, Sommer MOA. Spatial and temporal dynamics of SARS-CoV-2 in COVID-19 patients: A systematic review and meta-analysis. EBio Medicine, 2020; 58. DOI: 10.1016/j.ebiom.2020.102916.
27. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature, 2020; 581(7809): 465–9.
28. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectivity: When Is It Safe to Discontinue Isolation? Clin Infect Dis, 2021; 72(8): 1467–74.
29. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. Clin Infect Dis, 2020; 1–18.
30. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med, 2019; 381(24): 2293–303.
31. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med, 2020; 382(24): 2327–36.
32. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med, 2020; 382(19): 1787–99.
33. Whittington MD, Campbell JD. Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19 Institute for Clinical and Economic Review. Inst Clin Econ Rev, 2020; 1–18.
34. Gilead Sciences. An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. Gilead Sci. 2020 [cited 2020 Nov 7]. Available from: https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/an-open-letter-from-daniel-oday-chairman--ceo-gilead-sciences.