CoRe study: COVID-19 and remdesivir: An insight into the current health planning and policy

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ABSTRACT

Introduction: The ongoing coronavirus disease-2019 (COVID-19) pandemic has witnessed rampant use of the repurposed drug, remdesivir, despite its conflicting evidence and rapidly changing guidelines. Methods: A cross-sectional, country-wide, questionnaire-based, electronic survey was conducted among the healthcare professionals involved in COVID-19 management from April 18 to May 18, 2021. Results: Out of 231 responses, 185 were included. Significantly, greater knowledge of trials was reported by the frontline healthcare professionals compared to those who are not involved in COVID-19 care. Medicine practitioners and pulmonologists expressed greater willingness to continue remdesivir (Odds ratio (OR) 5.329, 95% Confidence interval (CI) 2.31–12.291 and 5.063, 95% CI 1.414–18.129, respectively). The rationale attributed was personal experience, current guidelines, non-availability of any alternate antiviral drug, expert recommendations, and local hospital policy either alone (20%, 8.1%, 5.9%, 2.7%, and 2.2%, respectively) or in combination (46.5%, 39.5%, 29.2%, 21.1%, and 15.7%, respectively). Awareness of evidence and knowledge of landmark studies made no statistically significant impact on clinical decision-making. Improved clinical outcomes were reported by 10/22 (45.4%) practitioners who used remdesivir for unconventional indications. Conclusion: The study throws critical insights into the current perspectives of doctors on remdesivir in clinical management and its potential impact on current health planning strategies.

Keywords: COVID-19, evidence-based medicine, guideline, remdesivir
pandemic, there was the emergence and resurgence of several new and repurposed drugs, which were based predominantly on biological plausibility and not on concrete evidence.[10] Amidst this struggle, a shimmer of hope came on May 1, 2020, when the United States Food and Drug Administration (FDA) granted emergency use authorization (EUA) to the repurposed drug, remdesivir, in the light of a preliminary report of a controlled clinical trial.[11,12] While the beginning was promising, further studies could not prove the unequivocal mortality or morbidity benefit of the drug.[13] Nevertheless, remdesivir did make its way to the treatment protocols and national guidelines of a significant proportion of the countries.[14,15] Subsequently, there was a massive upsurge of the use of remdesivir, leading to its acute shortage, with a consequent rise in black-marketing and enormous geo-political tension.[16,17] The hype from the drug, echoing what hydroxychloroquine did a year back, led to an unprecedented rise in public demand. All these were witnessed at a time when trials were still in their infancy and evidences were largely conflicting.

**Remdesivir and Its Evolution**

Remdesivir is a nucleoside analog prodrug whose antiviral activity is mediated by preferential incorporation of the molecule by viral ribonucleic acid (RNA)-dependent RNA polymerase into the RNA transcript, leading to delayed chain termination. In 2009, research programs for hepatitis C virus (HCV) and respiratory syncytial virus (RSV) led to the discovery of remdesivir.[18] Four years later, the drug’s activity against coronaviruses, namely, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) along with RSV, Marburg, and Ebola was identified. In a groundbreaking research, Wang et al demonstrated the effectiveness of remdesivir against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in an in-vitro study.[19] Two months later, Wang et al. in a randomized clinical trial (RCT) showed no statistically significant positive clinical outcomes compared to placebo.[20] Subsequent studies by Grein et al. and Olender et al. showed outcomes in favor of remdesivir.[21,22] The study by Goldman et al. showed a non-significant reduction in mortality rate, though the clinical improvement was significantly higher.[23] On a similar line, the meta-analysis by Al-Abdouh et al. on 7334 patients, disclosed no significant mortality benefit or time to clinical recovery but with higher rates of hospital discharge.[24] The meta-analysis by Rezagholizadeh et al. showed improved clinical outcomes on a 28-day recovery period, and a reduction in the need for invasive ventilation or extracorporeal membrane oxygenation; however, the sensitivity analysis did not reveal significant time to clinical improvement.[25] While many trials are still underway, the persistent variability in the outcome of the studies witnessed the repeated shuffling of remdesivir in and out of the management guidelines [Figure 1].[26,27]

**Background**

In order to cater to the massive burden of COVID-19 patients, particularly in developing countries with a meager doctor–patient ratio, medical practitioners trained in various clinical and allied fields had come together to serve the cause in the frontline. In this context, the mixed population of healthcare professionals along with the uncertainties of treatment, in the backdrop of dynamic and conflicting guidelines, formed a potential ground for deviation from evidence-based practice. Hence, a study assessing the current perspectives and practice of the healthcare professionals on remdesivir was felt as the need of the hour. This was a novel and first attempt in the medical literature, to address these issues in a hard-hit developing country. The study was conducted at a time when India was recording the highest number of daily infections and casualties throughout the globe.[28-31]

**Aims and Objectives**

This study aimed to analyze the current trends of evidence-based perspectives and practice among healthcare professionals of India involved in the management of COVID-19 on the use of remdesivir.

**Materials and Methods**

**Study design**

A cross-sectional, country-wide, observational study, based on an electronic survey method, was conducted among the healthcare professionals which included resident doctors, medical officers, and consultants (refer to the supplementary appendix for definitions) involved in the management of COVID-19.

**Study protocol, questionnaire, inclusion, and exclusion criteria**

A web-based questionnaire was formulated by a team of multidisciplinary healthcare professionals who were not only involved in the management of COVID-19 patients but also the various administrative services and COVID-19-related research projects. It was structured to encompass the various aspects of evidence-based perspectives and practice with regard to the use of remdesivir in COVID-19 using open- and close-ended questions. The nature and purpose of the study...
were elaborated at the beginning of the questionnaire. The identity and responses of the participants were kept confidential. Participation was voluntary and subjected to informed consent, which was in-built in the questionnaire. At the very first step, respondents involved in the management of COVID-19 were included. Any incompletely filled questionnaires and responses from undergraduate medical students and interns were excluded. Those not involved in the case management but not meeting the exclusion criteria were segregated into a control group [Figure 2].

The attitude was assessed based on whether the respondents use remdesivir in their clinical practice, willingness to continue its use, and cost-effectiveness. The current practice trends were identified based on the rationale to continue the use of the drug, unconventional indications for which they have been used, the subjective benefits observed, and the adverse events encountered. The respondents were entitled to a single response only. Post-submission editing of the responses was disabled. Each respondent was blinded to the response of the others.

Data collection
In the preliminary phase, the raw questionnaire was pilot tested among 10 randomly chosen healthcare professionals who were blinded to the study design. Their responses, with feedback, were obtained and the relevant changes were incorporated. Thus, validation was ensured (see supplementary appendix). Using the online platform of Google Forms, the questionnaire was effectively distributed across the various doctors’ forums, social media platforms, and web-based organizations. After obtaining ethical clearance, the questionnaire was circulated over a period of 30 days from April 18 to May 18, 2021 [Figure 2].

Outcome measures
The outcome measures were categorized into the three domains of knowledge, attitude, and practice. The measures were based on analysis of the knowledge-attitude-practice discordance among the doctors, reflecting on the various factors, in addition to EBM, which play a critical role in decision-making.

Figure 1: Depicting the mechanism of SARS-CoV-2 infection, mechanism of action of remdesivir and clinical trials, and meta-analysis on remdesivir as per chronology. Panel A: Molecular structure of remdesivir, prodrug, and active form including its pharmacokinetics, dosing recommendations, and common side effect profile. Panel B: Mechanism of SARS-CoV-2 infection and action of remdesivir on it. Panel C: Evolution of remdesivir based on early investigations in RSV and HCV, followed by subsequent use in novel coronavirus. Red colored outcome box is designated as unfavorable outcome, green represents favorable, whereas grey is of uncertain significance. The last part of its timeline shows ongoing trials on remdesivir.
Statistical analysis

The categorical variables were expressed as frequency (%) with 95% confidence intervals (CI) while the continuous variables were expressed as using means ± standard deviation (SD). Chi-square tests were applied to assess for the significance between independent and dependent variables. Further analysis between various dichotomous dependent and independent variables was carried out by using a multivariate binomial logistic regression model. Thus, the odds ratio (OR) with 95% CI was calculated and plotted on forest plots. The analyses were carried...
out with respect to the control group. A $P$ value of less than 0.05 was considered to be statistically significant. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 23 (International Business Machines Corporation (IBM)).

**Results**

**Participants and demographics**

A total of 231 responses were obtained, out of which 12 were excluded based on pre-defined inclusion and exclusion criteria. Of the remaining 219 responses, 34 of them, not involved in COVID-19 case management, were chosen as the control group. Subsequently, a total of 185 responses were considered for analysis. The country was stratified based on five major zones. The representations from north, south, east, west, and central zones were 45 (24.3%), 62 (31.6%), 41 (22.2%), 20 (10.8%), and 17 (9.2%), respectively. The majority of the healthcare professionals were from the fields of medicine which accounted for 109 out of 185 (58.9%) of the responses. This was followed by pulmonology 22 (11.9%), pediatrics 18 (9.7%), critical care medicine 17 (7.6%), and others 22 (11.9%) that included cardiology, neurology, nephrology, surgery, obstetricians, orthopedics, neurosurgery, radiology, oncology, surgery, and transfusion medicine who all have been involved as frontline healthcare workers. The majority of the respondents (125, 62.6%) were residents, which were followed by the consultants (54, 34.7%). The respondents had a mean duration of clinical practice of 6.4 ± 7.5 years with a clinical experience which varied from less than 5 years (103, 55.6%), between 5 and 10 years (52, 28.1%), and beyond 10 years (30, 16.2%), respectively.

**Excluded cases**

Out of the 12 excluded participants, three were undergraduate medical students not directly involved in the frontline, five responded partially, and four answered incorrectly in at least one of the landmark study outcome questions.

**The knowledge**

Out of 185 respondents, knowledge of at least one landmark study was present in 157 (84.9%) of them while 135 of them (73.0%) were aware of at least two landmark trials. Awareness regarding all four studies was present among 54 (29.2%) of the respondents. A total of 155 (83.8%) respondents stated that they were aware of the recent literature evidence of remdesivir. Active involvement in regular updates was reported by 133 (71.9%) healthcare professionals, while 39 (21.1%) were actively involved in the first wave only. Respondents from the fields of medicine and pulmonology had greater awareness of the recent evidence of remdesivir when compared to the control group (OR 7.185 (95% CI 5.945–12.791) and 4.000 (95% CI 1.117–14.324), respectively). With respect to the knowledge of trials, the respondents from all the fields had significantly greater awareness compared to the control group. Among them, medical practitioners and pulmonologists had significantly greater knowledge. OR for at least one landmark study among the medical practitioners and pulmonologists was 23.76 (95% CI 8.887–63.526), and 50.40 (95% CI 5.945–427.271), respectively, while for two landmark studies, it was 12.960 (95% CI 5.044–33.298) and 13.114 (95% CI 3.581–48.034), respectively. Medicine practitioners had statistically significant involvement with regard to the awareness of regular updates (OR 2.341, 95% CI 1.058–5.177). Analysis of the impact of duration of experience on clinical decision-making revealed no significant difference in the various subgroups (OR 0.913, 95% CI 0.347–2.399 in the less than 5 years group vs 2.514, 95% CI 0.969–6.525 in the 5–10 years group) [Figure 3].

**The attitude**

The current attitude of the healthcare professionals was highlighted in their responses to the questions, which enquired them about their perception of the benefits they have felt after using remdesivir over the past 1 year. Of the 185 respondents, 164 (88.6%) reported that they use remdesivir, among which 154 (83.2%) expressed their willingness to continue the same despite the evidence. Among the various fields, practitioners from medicine and pulmonology showed greater willingness to continue remdesivir with OR of 5.329 (95% CI 2.311–12.291) and 5.063 (95% CI 1.414–18.129), respectively. However, 22 (13.4%) of the respondents conveyed an unwillingness to continue the same. Cost-effectiveness was reported by 100 (54.1%) of the respondents [Figures 1, 3, and 4].

**The practice**

**Rationale and willingness to continue the use of remdesivir**

Among the respondents who preferred to continue therapy with remdesivir, 37 (20%) stated personal experience of perceived benefits as the sole rationale while 86 (46.5%) reported it to be one of the contributing factors. The other rationales, as stated, were guidelines alone (15, 8.1%), expert recommendations alone (5, 2.7%), local hospital policy alone (4, 2.2%), and non-availability of any alternative antiviral drug (11, 5.9%). As one of the contributing factors, guidelines (73, 39.5%), expert recommendations (39, 21.1%), absence of alternate drug (54, 29.2%), patient’s demand (31, 16.8%), local hospital policy (29, 15.7%), and personal review of the literature (6, 3.2%) showed higher proportions. With respect to guideline-based management, no statistically significant parameter had influenced the rationale of continuing the use of remdesivir as the OR with 95% CI for personal experience, expert’s recommendation, and absence of alternate drug was 0.574 (95% CI 0.086–3.834), 4.333 (95% CI 0.423–44.429), and 3.714 (95% CI 0.539–25.593), respectively. The OR for continuing the use of remdesivir was 5.329 (95% CI 5.329–12.291) for medicine, 5.063 (95% CI 1.414–18.129) for pulmonology, 4.125 (95% CI 0.974–17.469) for critical care medicine, and 2.925 (95% CI 0.853–10.025) for pediatrics. Awareness of evidence (OR 0.297, 95% CI 0.067–1.317), knowledge of at least one trial (OR 1.095, 95% CI 0.381–3.145), knowledge of
at least two trials (0.898, 95% CI 0.373–2.161), and knowledge of four landmark trials (OR 1.225, 95% CI 0.510–2.939) made no impact on the clinical decision-making on the future use of remdesivir [Figure 4, Table 1].

Unconventional use of Remdesivir
Of the 185 respondents, 15 (8.1%) medicine practitioners, 5 (2.1%) of critical medicine practitioners, and 2 (1.1%) from other fields of expertise reported use of the drug for unconventional indications like mild illness, diarrhea, end-stage renal disease, and pregnancy ($p = 0.12$). The improved outcome was reported in 10 (45.4%) of them. There was no statistically significant correlation between the decision to opt for unconventional use and engagement in regular updates (OR 0.817, 95% CI 0.313–2.136, $P = 0.68$). Field of expertise did not have statistically significant impact on unconventional indications ($p = 0.12$) neither were the years of clinical practice ($p = 0.965$) [Table 1].

Clinical response and adverse event profile
Out of 185 respondents, the various clinical parameters which were reported to have improved include oxygen saturation (84, 51.2%), fever spikes (50, 30.5%), cough (28, 17.1%), need for invasive ventilator support (79, 48.2%), mortality (52, 31.7%), radiological improvement (35, 21.3%), and curtailing the duration of intensive care unit (ICU) stay (83, 50.6%). With respect to the adverse event profile, transaminitis (15, 9.1%), acute kidney injury (12, 7.3%), and bradycardia (10, 6.1%) were reported. Other infrequent side effects as reported were hypotension, hyperuricemia, gastritis, hyperglycemia, infusion reaction, and anaphylaxis.

Discussion

EBM refers to the practice of judicious and explicit use of current best evidence in making decisions on clinical management. COVID-19 with its incredible pace of spread has thrown impeccable challenges to EBM. Multiple RCTs of remdesivir which were published revealed conflicting results. Despite the dearth of concrete evidence, there was a massive upsurge in the demand for the drug with intense geo-political and socio-economic impact. As of April 2021, remdesivir featured in all the major guidelines of the globe including those of the NIH, Infectious Disease Society of America (IDSA), NICE, and Indian Council of Medical Research (ICMR) as a conditional recommendation with the notable exception of WHO. There is no data to date on the perspectives of frontline healthcare professionals on the current knowledge, attitude, and practice trends on the use of remdesivir in this global crisis.

Key findings of the study
The majority of the frontline healthcare professionals expressed their willingness to continue the use of remdesivir. While the rationale extended across a wide spectrum of factors, the major
reasons were attributed to personal experience either alone or as a contributing factor, guidelines’ based management, and the non-availability of any alternative antiviral drug. Our analysis enlightened on the fact that no single factor was attributable to the decision-making process with regard to the continuation of remdesivir. Years of clinical experience, awareness, and knowledge of landmark studies made no statistically significant impact on the clinical decision-making to continue the use of remdesivir. The majority of the doctors who have used the drug for unconventional indications reported subjective clinical improvement. The adverse event profile was consistent with the known side effects of the drug.
Table 1: Demographic characteristics and perceptions of the participants

### Part A: Demographics (n=185)

| Variables                        | Frequency             |
|----------------------------------|-----------------------|
| **Field of expertise**           |                      |
| Medicine                         | 109 (58.9%)           |
| Pulmonology                      | 22 (11.9%)            |
| Pediatrics                       | 18 (9.7%)             |
| Critical care medicine           | 14 (7.6%)             |
| Others                           | 22 (11.9%)            |
| **Years of clinical practice**   |                      |
| Mean±SD (years)                  | 6.4±7.5               |
| >5 years                         | 103 (55.6%)           |
| 5-10 years                       | 52 (28.1%)            |
| >10 years                        | 30 (16.2%)            |
| **Level of expertise**           |                      |
| Resident                         | 125 (62.6%)           |
| Consultant                       | 54 (34.7%)            |
| Medical officer                  | 6 (2.6%)              |
| **Zonal representation of respondents across India** |       |
| Northern zone                    | 45 (24.3%)            |
| Southern zone                    | 62 (31.6%)            |
| Eastern zone                     | 41 (22.2%)            |
| Western zone                     | 20 (10.8%)            |
| Central zone                     | 17 (9.2%)             |

### Part B: Perceptions among the participants

| Variables                        | Frequency             |
|----------------------------------|-----------------------|
| **The knowledge (n=185)**        |                      |
| Respondents with knowledge of at least one trial | 157 (84.9%) |
| Respondents with knowledge of two or more trials | 135 (73.0%) |
| Respondents with knowledge of all four trials | 54 (29.2%) |
| Awareness regarding remdesivir evidences | 155 (83.8%) |
| Involvement in regular updates | 133 (71.9%) |
| Involvement in updates in the first wave only | 39 (21.1%) |
| **The attitude (n=185)**         |                      |
| Uses remdesivir                  | 164 (88.6%)           |
| Willingness to continue using remdesivir | 154 (83.2%) |
| Uses remdesivir but not willing to continue | 22 (13.4%) |
| Cost-effectiveness               | 100 (54.1%)           |

### The practice (n=185)

| Rationale to continue the practice of remdesivir | Alone | As one of the contributing factors |
|--------------------------------------------------|-------|------------------------------------|
| Personal experience of benefits                   | 37 (20%) | 86 (46.5%)                        |
| Current guidelines based                         | 15 (8.1%) | 73 (39.5%)                        |
| Expert recommendations                           | 5 (2.7%)  | 39 (21.1%)                        |
| Local hospital policy                            | 4 (2.2%)  | 29 (15.7%)                        |
| Absence of other antiviral options apart from remdesivir | 11 (5.9%) | 54 (29.2%)                        |
| Personal review of literature                    | ----    | 6 (3.2%)                          |
| Patient's demand                                 | ----    | 31 (16.8%)                        |

### Unconventional use of remdesivir (n=22)

| Variables                                      | Remarks |
|------------------------------------------------|---------|
| **Field of practice**                          |         |
| Medicine                                       | 15 (8.1%) | P=0.12 |
| Critical care medicine                         | 5 (2.7%)  |       |
| Other fields of expertise                      | 2 (1.1%)  |       |
| Pulmonologists and pediatricists               | ---      |       |
| **Clinical experience**                        |         |
| <5 years of clinical experience                | 12 (6.5%) |       |
| 5-10 years of clinical experience             | 6 (3.2%)  |       |
| >10 years of clinical experience               | 4 (2.2%)  |       |
| Involvement in updates                         |         |

*Contd...*
The impact and future directions

Our research has served to throw critical insights into the discrepancy between the current evidence and the clinical practice. The studied drug remdesivir stands today as a symbolic representation of the multitude of experimental therapeutic options, which are being tried in this ongoing devastating pandemic. The management principles in these testing times have been significantly backed up by clinical intuition, self-perceived benefits, and patient’s demand in addition to the dynamic clinical guidelines. Martinez-Sanz et al. highlighted similar factors in clinical decision-making in the early days of the COVID-19 pandemic. The fact that our study showed no impact of knowledge, years of clinical experience, and awareness of the evidence on the clinical decision-making with regard to the continuation of remdesivir has effectively served to emphasize the current knowledge-attitude-practice discordance which is widely existent and playing a crucial role in decision-making. The massive demand–supply mismatch of the drug in the context of failing pieces of evidence and rapidly changing guidelines is a clear reflection of this discordance.

Limitations

Our study relied on the dissemination of online questionnaires across various web-based platforms to reach the healthcare professionals, which incorporates a risk of selection bias. Secondly, given the large number of healthcare professionals involved in the direct management of COVID-19, our study catered to a limited number of doctors. Despite a wide distribution of respondents across various states of the country, the representation was unequal which hindered region-based analysis of the knowledge, attitude, and practice.

Conclusion

COVID-19 has affected all the sectors of the healthcare infrastructure of the country. Primary health care caters to the healthcare needs of a massive proportion of our country’s population. Hence, it is important to abide by the...
current knowledge and EBM while managing these cases. Our study was conducted to increase awareness regarding this knowledge-practice gap, which can have enormous implications in management. Our efforts to balance the evidence and the practice will hopefully lead us to a brighter future in the days to come.

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Conflicts of interest
There are no conflicts of interest.

References
1. Carley S, Horner D, Body R, Mackway‑Jones K. Evidence‑based medicine and COVID‑19: What to believe and when to change. Emerg Med J 2020;37:572‑5.
2. Editorials. Fix medicine’s evidence pipeline. Nature 2021;593:168.
3. Coronavirus (COVID‑19) Update: FDA Issues Emergency Use Authorization for Potential COVID‑19 Treatment [Internet]. U.S. Food and Drug Administration. Available from: https://www.fda.gov/news-events/press‑announcements/coronavirus‑covid‑19‑update‑fda‑issues‑emergency‑use‑authorization‑potential‑covid‑19‑treatment. [Last accessed on 2022 Apr 23].
4. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID‑19: A randomised, double‑blind, placebo‑controlled, multicentre trial. Lancet 2020;395:1569‑78.
5. Siemieniuk RAC, Bartoszko JJ, Ge L, Zeraatkar D, Iczovich A, Kum E, et al. Drug treatments for covid‑19: Living systematic review and network meta‑analysis. BMJ 2020;370:m2980.
6. Rochwerg B, Agarwal A, Zeng L, Leo YS, Appiah JA, Agoritsas T, et al. Remdesivir for severe covid‑19: A clinical practice guideline. BMJ 2020;370:1‑10.
7. First COVID‑19 treatment recommended for EU authorisation | European Medicines Agency. https://www.ema.europa.eu/en/news/first‑covid‑19‑treatment‑recommended‑eu‑authorisation. Available from: https://www.ema.europa.eu/en/news/first‑covid‑19‑treatment‑recommended‑eu‑authorisation. [Last accessed on 2022 Apr 23].
8. Indian demand for COVID‑19 drug remdesivir rising sharply · Cipla [Internet]. https://www.reuters.com/article/health‑coronavirus‑india‑cipla‑idUSKBN27P0TX. [Last accessed on 2022 Apr 23].
9. Inside the treacherous black market for Remdesivir in India— from private hospitals to distributors | Business Insider India. Available from: https://www.businessinsider.in/science/health/news/how‑remdesivir‑drug‑black‑market‑working‑in‑india/articleshow/82210121.cms. [Last accessed on 2021 May 28].
10. Eastman RT, Roth JS, Brimacombe KR, Sineonov A, Shen M, Patnaik S, et al. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID‑19. ACS Cent Sci 2020;6:672‑83.
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;30:269‑71.
12. 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;382:2327‑36.
13. Olender SA, Perez KK, Go AS, Balani B, Price‑Haywood EG, Shah NS, et al. Remdesivir for severe coronavirus disease 2019 (COVID‑19) versus a cohort receiving standard of care. Clin Infect Dis 2021;73:e4166‑74.
14. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid‑19. N Engl J Med 2020;383:1827‑37.
15. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez 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 2020;324:1048‑57.
16. 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;383:1813‑26.
17. WHO Solidarity Trial Consortium; Pan H, Peto R, Henao‑Restrepo A‑M, Preziosi M‑P, Sathiyaamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid‑19 — Interim WHO solidarity trial results. N Engl J Med 2021;384:497‑511.
18. 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;4:81‑2.
19. 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;101:106272.
20. Rezagholizadeh A, Khiali S, Sarbakhsh P, Entezari‑Maleki T. Remdesivir for treatment of COVID‑19: An updated systematic review and meta‑analysis. Eur J Pharmacol 2021;897:173926.
21. Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS‑5734 TM) in Participants From Birth to<18 Years of Age With Coronavirus Disease 2019 (COVID‑19)‑Full Text View‑ClinicalTrials.gov. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04431453. [Last accessed on 2021 May 28].
22. ACTIV‑5/Big Effect Trial (BET‑B) for the Treatment of COVID‑19‑Full Text View‑ClinicalTrials.gov. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04583969. [Last accessed on 2021 May 28].
23. Novel Coronavirus disease (COVID‑19), situation report‑64. Available from: https://cdn.who.int/media/docs/default‑source/wrindia/situation‑report/india‑situation‑report‑64.pdf?sfvrsn=f73932b4_4. [Last accessed on 2021 May 28].
24. Novel Coronavirus disease (COVID‑19), situation report‑65. Available from: https://cdn.who.int/media/docs/default‑source/wrindia/situation‑report/india‑situation‑report‑65.pdf?sfvrsn=f73932b4_4. [Last accessed on 2021 May 28].
25. Novel Coronavirus disease (COVID‑19), situation report‑66. Available from: https://cdn.who.int/media/docs/default‑source/wrindia/situation‑report/india‑situation‑report‑66.pdf?sfvrsn=f73932b4_4. [Last accessed on 2021 May 28].
26. Novel Coronavirus disease (COVID‑19), situation report‑67. Available from: https://cdn.who.int/media/docs/default‑source/wrindia/situation‑report/india‑situation‑report‑67.pdf?sfvrsn=f73932b4_4. [Last accessed on 2021 May 28].
 india‑situation‑report‑67.pdf?sfvrsn=f73932b4_4. [Last accessed on 2021 May 28].

27. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn’t. BMJ 1996;312:71‑2.

28. Pandey V. India coronavirus: Desperate Covid‑19 patients turn to black market for drugs. BBC News 2021; 16 Apr. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2010392914&from=export.

29. Living guidance for clinical management of COVID‑19 [Internet]. Who.int. 2022. Available from: https://www.who.int/publications/i/item/WHO‑2019‑nCoV‑clinical‑2021‑2. [Last accessed on 2022 Apr 23].

30. Covid.aiims.edu. 2022. Available from: https://covid.aiims.edu/wp‑content/uploads/2021/04/ COVID19ManagementAlgorithm22042021v1.pdf. [Last accessed on 2022 Apr 23].

31. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID‑19. Clin Infect Dis 2020;ciaa478. doi:10.1093/cid/ciaa478.

32. Overview | COVID‑19 rapid guideline; managing COVID‑19 | Guidance | NICE [Internet]. Nice.org.uk. 2022. Available from: https://www.nice.org.uk/guidance/ng191. [Last accessed on 2022 Apr 23].

33. COVID‑19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID‑19) Treatment Guidelines. National Institutes of Health. Available from: https://www.covid19treatmentguidelines.nih.gov/. [Last accessed on 2021 May 28].

34. Martínez‑Sanz J, Pérez‑Molina JA, Moreno S, Zamora J, Serrano‑Villar S. Understanding clinical decision‑making during the COVID‑19 pandemic: A cross‑sectional worldwide survey. EClinicalMedicine 2020;27:100539.

35. Piscoya A, Ng‑Sueng LF, del Riego AP, Cerna‑Viacava R, Pasupuleti V, Roman YM, et al. Efficacy and harms of remdesivir for the treatment of COVID‑19: A systematic review and meta‑analysis. PLoS One 2020;15:1‑19. Available from: http://dx.doi.org/10.1371/journal.pone.0243705.

36. Shrestha DB, Budhathoki P, Syed N‑I‑H, Rawal E, Raut S, Khadka S. Remdesivir: A potential game‑changer or just a myth? A systematic review and meta‑analysis. Life Sci 2021;264:118663.
**SUPPLEMENTARY APPENDIX**

**CoRe Study: COVID-19 and Remdesivir: An insight into the current health planning and policy**

**Content**

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**Definitions:**

In the study, levels of medical expertise are stratified as a medical student, intern, resident, consultant, and medical officer.

Medical student: An individual who is enrolled in a medical school and pursuing undergraduate medical education, still not passed final under graduation examination.

Medical intern: An individual who has cleared the final undergraduate medical examination and under supervised clinical training in a hospital, before getting his/her permanent medical council registration.

Resident: An individual healthcare professional who is enrolled in a postgraduate training program of specific medical specialties and who works under supervision.

Consultant: Any post postgraduate medical personnel who is practicing independently.

Medical officer: Any medical graduate after his/her postgraduation, practicing independently.

Regarding the use of remdesivir, unconventional indications are defined as any indication that is outside the purview of regional or national–international guidelines.

**Pilot study**

The preliminary questionnaire was circulated among 10 frontline healthcare professionals. The responses were reviewed and suggestions were incorporated.

**Pilot questionnaire**

Consent:

Name of the Indian state of practice

Level of expertise
- Consultant
- Resident
- Medical student
- Medical officer
- Intern
- Others

Field of expertise
- Medicine
- Pulmonologist
- Pediatrician
- Anesthesia
- ENT
- Others
Are you involved in COVID-19 case management?
- Yes
- No
- Others

Do you use remdesivir for your patients?
- Yes
- No
- Others

Are you aware of the latest evidences of remdesivir in COVID-19?
- Yes
- No
- Others

Are you aware of the ACTT-1 trial on remdesivir?
- Yes
- No
- Other

Are you aware of WHO’s Solidarity trial on remdesivir?
- Yes
- No
- Others

Are you aware of the results of randomized control trial (RCT) on remdesivir in COVID-19, published in the Lancet by Wang et al.?
- Yes
- No
- Others

Did ACTT-1 RCT (NEJM) show superiority of remdesivir over placebo in terms of shortening the time to recovery? (Kindly go through the trial depiction and then answer)
- Yes
- No
- Others

Did RCT by Wang et al. (Lancet) show any difference in time to clinical improvement? (Kindly go through the trial depiction and then answer)
- Yes
- No
- Others

Did the Solidarity trial show any mortality benefit? (Kindly go through the trial depiction and then answer)
- Yes
- No
- Others

Why do you want to continue using remdesivir in COVID-19, when evidences are not supporting its use? (Multiple options can be opted)
- Guidelines of the state/central institute of excellence
- Personal experience of benefit
- Expert’s recommendation
- Patient’s demand
- Hospital’s recommendation
- Will not continue to use
- Pre-clinical studies showed benefits
- No other available options as antiviral other than remdesivir
- Personal literature review
- Others

If the answer to the above question is yes, please specify the outcome of it.
Which parameter(s) according to you improves after remdesivir based on your experience? (Multiple options can be opted)
- Oxygen saturation (SpO2)
- Fever
- Cough
- Need for invasive ventilation
- Reduced ICU stay
- Radiological improvement
- Reduced mortality
- No added benefit
- Others

Did any of your patients have any adverse drug reactions with remdesivir?
- Yes
- No

Does the benefit of using remdesivir outweighs the cost of therapy?
- Yes
- No

Specify any adverse drug reaction, if any
No

Any other remarks or suggestions, you are welcome

Table S1: Summary of suggestions from the pilot study

| Respondents | Suggestions given |
|-------------|-------------------|
| 1           | Incorporation of years of clinical practice |
| 2           | Addition of meta-analysis by Siemieniuk et al. to the study questionnaire |
| 3           | No suggestions given |
| 4           | No suggestions given |
| 5           | To include a question on personal experience on the unconventional use of remdesivir |
| 6           | Inclusion of involvement in regular updates |
| 7           | No suggestions given |
| 8           | No suggestions given |
| 9           | No suggestions given |
| 10          | No suggestions given |

Final questionnaire:

CoRe study: COVID-19 and remdesivir: An insight into the current health planning and policy: Remdesivir and Healthcare professionals In Pandemic - Perspectives of Emerging Evidence. This is an epidemiological study to evaluate the change in practice based on emerging evidences during COVID-19 pandemic. This survey will enhance knowledge sharing and promote evidence-based care during COVID-19 Pandemic: The Second Wave. Help medical literature to flourish by contributing your precious few minutes.”

Individuals’ identities will be confidential.
Did ACTT-1 RCT (NEJM) show superiority of remdesivir over placebo in terms of shortening the time to recovery? (Kindly go through the trial depiction and then answer)

- Yes
- No
- Others

Did RCT by Wang et al. (Lancet) show any difference in time to clinical improvement? (Kindly go through the trial depiction and then answer)

- Yes
- No
- Others

Did the Solidarity trial show any mortality benefit? (Kindly go through the trial depiction and then answer)

- Yes

Did a meta-analysis published in BMJ show any benefit of remdesivir on mortality, mechanical ventilation, length of hospital stay, and duration of symptoms with certainty? (Kindly go through the study depiction and then answer)

- Yes
- No
- Others

Do you periodically update yourself to the changing guidelines of COVID-19 management by your state or central health departments? (Multiple options can be opted)

- Yes
- No
- Yes, I did in the first wave
- Others

Do you want to continue using remdesivir in your patients with COVID-19?

- Yes
- No
- Others

Why do you want to continue using remdesivir in COVID-19, when evidences are not supporting its use? (Multiple options can be opted)

- Guidelines of the state/central institute of excellence
- Personal experience of benefit
- Expert's recommendation
- Patient's demand
- Hospital's recommendation
- Will not continue to use
- Pre-clinical studies showed benefits
- No other available options as antiviral other than remdesivir
- Personal literature review
- Others

Have you given remdesivir outside the conventional indications?

- Yes
- No
If the answer to the above question is yes, please specify the outcome of it.

Which parameter(s) according to you improves after remdesivir based on your experience? (Multiple options can be opted)

- SpO2
- Fever
- Cough
- Need for invasive ventilation
- Reduced ICU stay
- Radiological improvement
- Reduced mortality
- No added benefit
- Others

Did any of your patients have any adverse drug reactions with remdesivir?

- Yes
- No

Does the benefit of using remdesivir outweighs the cost of therapy?

- Yes
- No

Specify any adverse drug reaction, if any

No

Any other remarks or suggestions, you are welcome
Table S1: Rationale based on various parameters

|                          | Personal experience of benefit | Guidelines | Expert's recommendation | Local hospital policy | No other available options of antiviral other than remdesivir | Patient's demand | Personal review of literature | Benefits from pre-clinical studies | Unwilling to use |
|--------------------------|-------------------------------|------------|-------------------------|----------------------|--------------------------------------------------------------|------------------|--------------------------------|--------------------------------------|------------------|
| Medicine                 | 24.3                          | 22.7       | 11.9                    | 8.1                  | 16.2                                                         | 10.3             | 2.2                           | 3.2                   | 10.3             |
| Pulmonology              | 8.1                           | 3.8        | 2.7                     | 3.2                  | 2.7                                                          | 2.2              | 0                             | 1.6                   | 2.2              |
| Pediatrics               | 3.2                           | 2.7        | 1.1                     | 1.1                  | 4.3                                                          | 1.1              | 1.1                           | 1.1                   | 2.7              |
| Critical care medicine   | 4.9                           | 4.3        | 2.2                     | 0.5                  | 2.7                                                          | 1.1              | 0                             | 0.5                   | 1.6              |
| Other fields of expertise| 5.9                           | 5.9        | 3.2                     | 2.7                  | 3.2                                                          | 2.2              | 0                             | 0                     | 0                |
| Resident                 | 23.2                          | 27.6       | 15.1                    | 11.4                 | 20                                                           | 9.7              | 11.1                          | 4.9                   | 11.9             |
| Consultant               | 21.6                          | 11.4       | 4.9                     | 4.3                  | 8.6                                                          | 6.5              | 2.2                           | 1.6                   | 4.9              |
| Medical officer          | 1.6                           | 0.5        | 1.1                     | 0                   | 0.5                                                         | 0.5              | 0                             | 0                     | 0                |
| Clinical experience of <5 years | 22.7                 | 21.1       | 10.8                    | 7.6                  | 14.6                                                        | 8.6              | 1.6                           | 6.4                   | 6.5              |
| Clinical experience of 5-10 years | 14.6                 | 11.9       | 8.6                     | 5.9                  | 9.7                                                         | 3.2              | 1.1                           | 0                     | 2.7              |
| Clinical experience of more than 10 years | 9.2                 | 6.5        | 1.6                     | 2.2                  | 14.9                                                        | 4.9              | 0.5                           | 1.1                   | 4.9              |
| Knowledge of at least one landmark trial | 41.1                 | 34.1       | 17.3                    | 14.1                 | 24.3                                                        | 16.2             | 3.2                           | 5.4                   | 14.1             |
| Knowledge of ≥2 landmark trials | 37.3                 | 28.1       | 14.1                    | 11.4                 | 19.5                                                        | 13               | 2.7                           | 4.3                   | 12.4             |
| Knowledge of four landmark trials | 16.8                 | 11.4       | 6.5                     | 7.6                  | 9.2                                                         | 5.9              | 1.1                           | 0.5                   | 2.2              |