Antiviral Drugs That Are Under Evaluation for the Treatment of COVID-19

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Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.**

For more information on the antiviral agents that are currently being evaluated for the treatment of COVID-19, see Table 2.

Remdesivir

The Remdesivir section of the Guidelines will be updated soon. See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without corticosteroids.

Recommendation for Prioritizing Limited Supplies of Remdesivir

- Because remdesivir supplies are limited, the Panel recommends prioritizing **remdesivir** for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BI)**.

Recommendation for Patients With Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Recommendations for Patients with COVID-19 Who Require Supplemental Oxygen

For Patients Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of **remdesivir** therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Chloroquine or Hydroxychloroquine With or Without Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.

Ivermectin
• The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Antiviral Therapy

Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.[1] Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease, including critical illness.[2] For this reason, it is necessary to understand the role of antivirals in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.

The following sections describe the underlying rationale for using different antiviral medications, provide the Panel's recommendations for using these medications to treat COVID-19, and summarize the existing clinical trial data. Additional antiviral therapies will be added to this section of the Guidelines as new evidence emerges.

References

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Remdesivir

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Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2]

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies.

Remdesivir is available through the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for people with severe COVID-19.

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends prioritizing remdesivir for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).**

Recommendation for Patients With Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Recommendations for Patients With COVID-19 Who Require Supplemental Oxygen

For Patients Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some

experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Rationale

The recommendations for remdesivir are largely based on data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT-1]). This trial included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days (or until hospital discharge, whichever came first).

Participants who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time was 11 days vs. 15 days, respectively).[3]

For Patients Who Do Not Require Supplemental Oxygen

In the preliminary subgroup analyses of ACTT-1, there was no observed benefit for remdesivir in people with COVID-19 who did not require supplemental oxygen; however, the number of people in this category was relatively small. Remdesivir is being evaluated in another clinical trial for the treatment of patients with moderate COVID-19; complete data from this trial are expected soon.

For Patients Who Require Supplemental Oxygen But Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

The preliminary analysis of ACTT-1 also reported that the participants with the clearest evidence of clinical benefit from starting remdesivir were those who required supplemental oxygen but who did not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO at baseline (n = 421). In this subgroup, those who received remdesivir had a shorter time to recovery than those who received placebo (recovery rate ratio 1.47; 95% CI, 1.17–1.84); in a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit (HR for death 0.22; 95% CI, 0.08–0.58).

For Patients Who Require Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation

In patients who required delivery of oxygen through a high-flow device or noninvasive ventilation at baseline (n = 197), there was no observed difference in the time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38). However, because the trial was not powered to detect differences in outcomes within these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

For Patients Who Require Invasive Mechanical Ventilation or ECMO

In participants who were on invasive mechanical ventilation or ECMO at baseline (n = 272), there was no observed difference in the time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).

Overall, a review of the final data set, which included 28-day mortality, showed that this data set was consistent with the published preliminary data (the unpublished data was provided to the Panel by the ACTT-1 study team [written communication, July 2020]).

For patients with COVID-19 who required delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, there was no observed difference between the remdesivir and placebo groups in the time to recovery or the mortality rate. However, because the trial was not powered to detect differences in outcomes within these subgroups, there is uncertainty as to whether starting remdesivir confers clinical benefit in these patients. For this reason, the Panel cannot make a recommendation either for or against starting remdesivir in these patients. Because the supply of remdesivir is limited, the Panel recommends prioritizing the drug for use in those for whom efficacy has been demonstrated (i.e., in hospitalized patients who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO).

Duration of Therapy

Data from a multinational, open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit.[4] The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts consider extending the total treatment duration of remdesivir to up to 10 days in patients who do not improve after 5 days of remdesivir therapy.[5]

See Remdesivir: Selected Clinical Data for more information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio).

Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters.

Remdesivir may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction may modestly reduce remdesivir levels. The clinical relevance of lower remdesivir levels is unknown.[6] Based on information provided by Gilead Sciences (written communication, July 2020), the use of remdesivir with drugs that are strong inducers (e.g., rifampin) **is not recommended**.

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020). Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[7]

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an estimated glomerular filtration rate (eGFR) of <50 mL/min are excluded from some clinical trials (some trials have an eGFR cutoff of <30 mL/min).

Considerations in Pregnancy

- Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus.[5]
- The safety and effectiveness of remdesivir for the treatment of COVID-19 have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

- Remdesivir is available through the FDA EUA for adults and children and through compassionate use programs for pregnant women and children with COVID-19.
- Ninety-eight female participants received remdesivir as part of a randomized controlled trial for the treatment of Ebola virus infection; six of these participants had a positive pregnancy test. The obstetric and neonatal outcomes were not reported in the study.[8]

Considerations in Children

- The safety and effectiveness of remdesivir for the treatment of COVID-19 have not been evaluated in pediatric patients.
- Remdesivir is available through an FDA EUA for adults and children and through compassionate use programs for children with COVID-19. A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier NCT04431453).
- In the same randomized controlled trial for the treatment of Ebola virus infection discussed above, 41 pediatric patients received remdesivir. These patients included neonates and children aged <18 years.[8] The safety and clinical outcomes for children were not reported separately in the published results for the trial. One neonate received remdesivir for the treatment of vertically transmitted Ebola virus infection and recovered.[9]

Clinical Trials

Multiple clinical trials that are evaluating remdesivir are currently underway or in development. Please check *ClinicalTrials.gov* for the latest information.

References

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Remdesivir: Selected Clinical Data

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Remdesivir is an investigational antiviral agent. It is not approved by the Food and Drug Administration, but it is available by Emergency Use Authorization for the treatment of hospitalized patients with severe COVID-19.

The information presented in this section may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see *ClinicalTrials.gov* for more information on clinical trials that are evaluating remdesivir.

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

The Adaptive COVID-19 Treatment Trial (ACTT-1) is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial.[1] The primary study endpoint was time to clinical recovery. Severity of illness at baseline and at Day 15 was assessed using an eight-point ordinal scale:

1. Not hospitalized, no limitations
2. Not hospitalized, with limitations
3. Hospitalized, no active medical problems
4. Hospitalized, not on oxygen
5. Hospitalized, on oxygen
6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation
7. Hospitalized, on mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8. Death

Study Population

- The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients were enrolled if they met at least one of the following conditions:
  - The patient had pulmonary infiltrates, as determined by radiographic imaging;
  - Saturation of oxygen (SpO_2) was ≤94% on room air;
  - The patient required supplemental oxygen;
  - The patient was on mechanical ventilation; *or*
  - The patient was on ECMO.
- The study excluded individuals who had alanine transaminase (ALT) or aspartate transaminase (AST) levels >5 times the upper limit of normal (ULN), those who had an estimated glomerular filtration rate <30 mL/min, and those who were pregnant or breastfeeding.

Preliminary Results

- Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis.
- The median time from symptom onset to randomization was 9 days (IQR 6–12 days).

- Remdesivir significantly reduced the time to recovery compared to placebo (median time to recovery was 11 days vs. 15 days; recovery rate ratio 1.32; 95% CI, 1.12–1.55; $P < 0.001$).
- Clinical improvement based on the ordinal scale outlined above was significantly higher at Day 15 in patients who received remdesivir than in those who received placebo (OR 1.50; 95% CI, 1.18–1.91, $P < 0.001$).
- The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 421; recovery rate ratio 1.47; 95% CI, 1.17–1.84). In a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.22; 95% CI, 0.08–0.58).
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 197), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.20, 95% CI, 0.79–1.81). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).
- Among the patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).
- Among patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the remdesivir and placebo groups. Mild to moderate disease was defined as SpO_2 >94% on room air and a respiratory rate of <24 breaths/min without supplemental oxygen.
- The mortality estimate by Day 14 was lower in the remdesivir arm than in the placebo arm (7.1% vs. 11.9%), but the difference was not statistically significant (HR 0.70; 95% CI, 0.47–1.04).
- The use of remdesivir was associated with shorter time to recovery, regardless of the duration of symptoms prior to randomization (≤10 days vs. >10 days).
- The percentages of participants with serious adverse effects (AEs) were similar in the remdesivir and placebo groups (21.1% vs. 27.0%).
- Transaminase elevations occurred in 4.1% of remdesivir recipients and 5.9% of placebo recipients.

Limitations

At the time of publication, the full dataset was not available for analysis. This summary will be updated when the final analyses are published.

Interpretation

In patients with severe COVID-19, remdesivir reduced the time to clinical recovery. The benefit of remdesivir was most apparent in hospitalized patients who only required supplemental oxygen. There was no observed benefit of remdesivir in those who were on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. There was no observed benefit of remdesivir in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Multinational, Randomized Trial of Different Durations of Remdesivir Treatment in Hospitalized Patients

This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of intravenous (IV) remdesivir. The primary study endpoint was clinical status at Day 14, which was assessed using a seven-point ordinal scale:[2]

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for remdesivir administration)
7. Not hospitalized

Study Population

- The study enrolled hospitalized patients aged ≥12 years with confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates.
- Patients in this study had either SpO_2 ≤94% on room air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated creatinine clearance <50 mL/min.

Results

- Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of remdesivir treatment.
- At baseline, participants in the 10-day group had worse clinical status (based on ordinal scale distribution) than those in the 5-day group ($P = 0.02$).
- After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups ($P = 0.14$)
- The time to clinical improvement of at least two levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days).
- The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10 days) and 10-day group (8 days; IQR 5–10 days).
- Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%). Four percent of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs.

Limitations

- This was an open-label trial without a placebo control group, so the clinical benefit of remdesivir could not be assessed.

- There were baseline imbalances in the clinical status of participants in the 5-day and 10-day groups.

Interpretation

In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, remdesivir treatment for 5 or 10 days had similar clinical benefit. Because this trial excluded patients who were on mechanical ventilation, the appropriate duration of remdesivir treatment for critically ill patients is still unclear.

Randomized Controlled Trial of Remdesivir Versus Placebo for Severe COVID-19 in China

This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China. Patients were randomized 2:1 to receive IV remdesivir or normal saline placebo for 10 days. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.[3]

Study Population

- This study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days. These patients had SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg and radiographically confirmed pneumonia.

Results

- In this study, 237 patients were randomized to receive remdesivir (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China.
- The median time from symptom onset to randomization was 9 days for the remdesivir group and 10 days for the placebo group.
- Sixty-five percent of the participants in the remdesivir group and 68% of the participants in the placebo group received corticosteroids.
- Twenty-eight percent of the participants in the remdesivir group and 29% of the participants in the placebo group received lopinavir/ritonavir.
- Twenty-nine percent of the participants in the remdesivir arm and 38% of the participants in the placebo arm received interferon alfa-2b.

Study Endpoints

- There was no difference in the time to clinical improvement between the remdesivir and placebo groups (median time to clinical improvement was 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75).
- For patients who started remdesivir or placebo within 10 days of symptom onset, a faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm (median of 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant.
- The 28-day mortality was similar for the two study arms (14% of participants in the remdesivir arm vs. 13% in the placebo arm).
- There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of

decline over time was similar between the two groups.

- The number of participants who experienced AEs was similar between the two groups (66% of participants in the remdesivir arm vs. 64% in the placebo arm).
- More participants in the remdesivir arm discontinued therapy due to AEs (12% of participants in the remdesivir arm vs. 5% in the placebo arm).

Limitations

- The study was terminated early because it did not reach its target enrollment; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes.
- The use of concomitant medications (i.e., corticosteroids, lopinavir/ritonavir, interferons) may have obscured the effects of remdesivir.

Interpretation

There was no difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between remdesivir-treated and placebo-treated patients; however, the study was underpowered to detect differences in these outcomes between the two groups.

References

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Chloroquine or Hydroxychloroquine With or Without Azithromycin

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Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, in addition to malaria. In general, hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine.

Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.[1] Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) to the cell receptor.[2] In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.[3] Both chloroquine and hydroxychloroquine also have immunomodulatory effects. It has been hypothesized that these effects are other potential mechanisms of action for the treatment of COVID-19. However, despite demonstrating antiviral activity in some in vitro systems, hydroxychloroquine with or without azithromycin did not reduce upper or lower respiratory tract viral loads or demonstrate clinical efficacy in a rhesus macaque model.[4]

Chloroquine and hydroxychloroquine, with or without azithromycin, have been studied in multiple clinical trials for the treatment of COVID-19. The recommendations below are based on an assessment of the collective evidence from these studies.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Rationale

The safety and efficacy of chloroquine and hydroxychloroquine with or without azithromycin have been evaluated in randomized clinical trials, observational studies, and single-arm studies. Please see Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data for more information.

In a large randomized controlled trial of hospitalized patients in the United Kingdom, hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Participants who were randomized to receive hydroxychloroquine had a longer median hospital stay than those who received the standard of care. In addition, among patients who were not on invasive mechanical ventilation at the time of randomization, those who received hydroxychloroquine were

more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.[5]

In another randomized controlled trial that was conducted in Brazil, neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin improved clinical outcomes among hospitalized patients with mild to moderate COVID-19. More adverse events occurred among patients who received hydroxychloroquine or hydroxychloroquine plus azithromycin than among those who received the standard of care.[6] Data from another randomized study of hospitalized patients with severe COVID-19 do not support using hydroxychloroquine plus azithromycin over hydroxychloroquine alone.[7]

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19. For example, in a large retrospective observational study of patients who were hospitalized with COVID-19, hydroxychloroquine use was not associated with a reduced risk of death or mechanical ventilation.[8] Another multicenter retrospective observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of a large cohort of hospitalized patients with COVID-19.[9] Patients who received hydroxychloroquine with or without azithromycin did not have a decreased risk of in-hospital mortality when compared to those who received neither hydroxychloroquine nor azithromycin.

Conversely, a large retrospective cohort study reported a survival benefit among hospitalized patients who received either hydroxychloroquine alone or hydroxychloroquine plus azithromycin, compared to those who received neither drug.[10] However, patients who did not receive hydroxychloroquine had a lower rate of admission to the intensive care unit, which suggests that patients in this group may have received less-aggressive care. Furthermore, a substantially higher percentage of patients in the hydroxychloroquine arms also received corticosteroids (77.1% of patients in the hydroxychloroquine arms vs. 36.5% of patients in the control arm). Given that the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that corticosteroids improve the survival rate of patients with COVID-19 (see Corticosteroids), it is possible that the findings in this study were confounded by this imbalance in corticosteroid use.[11] These and other observational and single-arm studies are summarized in Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data.

Many of the observational studies that have evaluated the use of chloroquine or hydroxychloroquine in patients with COVID-19 have attempted to control for confounding variables. However, study arms may be unbalanced in some of these studies, and some studies may not account for all potential confounding factors. These factors limit the ability to interpret and generalize the results from observational studies; therefore, results from these studies are not as definitive as those from large randomized trials. Given the lack of a benefit seen in the randomized clinical trials and the potential for toxicity, the Panel **recommends against** using hydroxychloroquine or chloroquine with or without azithromycin to treat COVID-19 in hospitalized patients **(AI)**.

The Panel also **recommends against** using high-dose chloroquine to treat COVID-19 **(AI)**. High-dose chloroquine (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days). A randomized clinical trial compared the use of high-dose chloroquine and low-dose chloroquine in hospitalized patients with severe COVID-19. In addition, all participants received azithromycin, and 89% of the participants received oseltamivir. The study was discontinued early when preliminary results showed higher rates of mortality and QTc prolongation in the high-dose chloroquine group.[12]

Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with COVID-19. However, other clinical trials are still ongoing.[13,14] In nonhospitalized

patients, the Panel **recommends against** the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial **(AI)**.

The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly.[15]

Please see Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data for additional details.

Adverse Effects

Chloroquine and hydroxychloroquine have a similar toxicity profile, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine.

Cardiac Adverse Effects

- QTc prolongation, Torsade de Pointes, ventricular arrythmia, and cardiac deaths.[16] If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse events, especially prolonged QTc interval **(AIII)**.
- The risk of QTc prolongation is greater for chloroquine than for hydroxychloroquine.
- Concomitant medications that pose a moderate to high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, macrolides [including azithromycin],[16] fluoroquinolone antibiotics)[17] should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
- Multiple studies have demonstrated that concomitant use of hydroxychloroquine and azithromycin can prolong the QTc interval;[18-20] in an observational study, the use of hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.[9] The use of this combination warrants careful monitoring.
- Baseline and follow-up electrocardiograms are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.[21]
- The risk-benefit ratio should be assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 bpm), or uncorrected hypokalemia and/or hypomagnesemia.

Other Adverse Effects

- Hypoglycemia, rash, and nausea. Divided doses may reduce nausea.
- Retinopathy. Bone marrow suppression may occur with long-term use, but this is not likely with short-term use.

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors. Use caution when administering these drugs with medications that are metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants, digoxin).[22] Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[23]

Considerations in Pregnancy

- Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE.
- Hydroxychloroquine exposure has not been associated with adverse pregnancy outcomes in ≥300 human pregnancies.
- A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis during pregnancy.
- No dose changes are necessary for chloroquine or hydroxychloroquine during pregnancy.

Considerations in Children

- Chloroquine and hydroxychloroquine have been routinely used in pediatric populations for the treatment and prevention of malaria and for rheumatologic conditions.

Drug Availability

- Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19.
- Hydroxychloroquine is approved by the FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. Chloroquine is approved for the treatment of malaria and extraintestinal amebiasis. Azithromycin is commonly used for the treatment and/or prevention of nontuberculous mycobacterial infection, various sexually transmitted infections, and various bacterial infections.

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Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

Last Updated: October 9, 2020

Chloroquine is approved by the Food and Drug Administration (FDA) for the treatment and prevention of malaria and for the treatment of extraintestinal amebiasis. Hydroxychloroquine is approved by the FDA for the treatment of lupus erythematosus, malaria, and rheumatoid arthritis. Azithromycin is commonly used for the treatment and/or prevention of mycobacterial (nontuberculous) infection, sexually transmitted infections, and various bacterial infections. Azithromycin has primarily been studied for the treatment of COVID-19 when it is used in combination with hydroxychloroquine. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial includes an azithromycin monotherapy arm, which is currently enrolling.

The information presented in this section may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see *ClinicalTrials.gov* for more information on clinical trials that are evaluating chloroquine, hydroxychloroquine, and azithromycin.

Randomized Controlled Trials

The Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary Results from a Multicenter, Randomized Controlled Trial

This study has not been peer reviewed.

RECOVERY is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received hydroxychloroquine. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients with prolonged QTc intervals were excluded from the hydroxychloroquine arm.

Patients were randomized in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus hydroxychloroquine or one of the other treatments in the platform trial. Patients in the hydroxychloroquine arm received a loading dose of hydroxychloroquine 800 mg at entry and at 6 hours, followed by hydroxychloroquine 400 mg every 12 hours for the next 9 days or until discharge. The primary outcome was all-cause mortality at Day 28 after randomization.

The trial enrollment ended early on June 5, 2020, after an independent data-monitoring committee recommended reviewing the unblinded data, and the investigators and trial-steering committee concluded that the data showed no beneficial effect of hydroxychloroquine.[1]

Patient Characteristics

- Of the 7,513 participants who were eligible for hydroxychloroquine, 1,561 were randomized to receive hydroxychloroquine and 3,155 were randomized to receive standard of care. The remaining participants were randomized to other treatment arms in the study.
- In both the hydroxychloroquine arm and the standard of care arm, the mean ages were 65 years; 41% of the participants were aged ≥70 years.
- Ninety percent of patients had laboratory-confirmed SARS-CoV-2 infection.
- Comorbidities were common; 57% of patients had at least one major comorbidity. Diabetes mellitus was present in 27% of patients, heart disease in 26%, and chronic lung disease in 22%.

- At randomization, 17% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.
- The use of azithromycin or another macrolide during the follow-up period was similar in both arms (17% vs. 19%), as was the use of dexamethasone (8% vs. 9%).

Results

- There was no significant difference in the primary outcome of 28-day mortality between the two arms; 418 patients (26.8%) in the hydroxychloroquine arm and 788 patients (25.0%) in the standard of care arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.96–1.23; $P = 0.18$).
- A similar 28-day mortality for hydroxychloroquine patients was reported during the post hoc exploratory analysis that was restricted to the 4,234 participants (90%) who had a positive SARS-CoV-2 test result.
- Participants in the hydroxychloroquine arm were less likely to survive hospitalization and had a longer median time to discharge than patients in the standard of care arm. In addition, participants who were randomized to receive hydroxychloroquine and who were not on invasive mechanical ventilation at baseline had an increased risk of requiring intubation and an increased risk of death.
- At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 698 patients (44.7%) in the hydroxychloroquine arm and 1,357 patients (43.0%) in the standard of care arm. There were no differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of atrioventricular block that required intervention.

Limitations

- The study was not blinded.
- Information on the occurrence of new major cardiac arrythmia was not collected throughout the entire trial period.

Interpretation

Hydroxychloroquine does not decrease 28-day all-cause mortality when compared to the usual standard of care in hospitalized persons with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Participants who were randomized to receive hydroxychloroquine had a longer median length of hospital stay, and those who were not on invasive mechanical ventilation at the time of randomization were more likely to require intubation or die during hospitalization if they received hydroxychloroquine.

Randomized Controlled Trial of Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin Among Hospitalized Patients with Mild or Moderate COVID-19 in Brazil

This study was an open-label, three-arm, randomized controlled trial that was conducted in Brazil. The study enrolled hospitalized patients aged ≥18 years with suspected or confirmed cases of mild or moderate COVID-19 and duration of symptoms ≤14 days.

Patients received either standard of care alone, hydroxychloroquine 400 mg twice daily for 7 days (plus standard of care), or hydroxychloroquine 400 mg twice daily plus azithromycin 500 mg daily for 7 days (plus standard of care). The primary outcome was clinical status at Day 15, as assessed by a seven-point ordinal scale among the patients with confirmed COVID-19 (modified intention to treat analysis). Exclusion criteria included the need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask, a history of ventricular tachycardia, or a QT interval ≥480 ms. Steroids, other immunomodulators, and

antiviral agents were allowed; 23.3% to 23.9% of patients received oseltamivir.[2]

Patient Characteristics

- The analysis included 504 patients with confirmed COVID-19.
- The mean patient age was 50 years, and 58% of patients were men.
- At baseline, 58.2% of patients were ordinal level 3 (hospitalized without oxygen), and 41.8% were ordinal level 4 (hospitalized with oxygen).
- The median time from symptom onset to randomization was 7 days.

Results

- There was no significant difference between the odds of worse clinical status at Day 15 for patients in the hydroxychloroquine group (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in the hydroxychloroquine plus azithromycin group (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$).
- There were no significant differences in the secondary outcomes of the three arms, including progression to mechanical ventilation during the first 15 days and mean number of days "alive and free of respiratory support."
- A greater proportion of patients who received hydroxychloroquine plus azithromycin (39.3%) or hydroxychloroquine alone (33.7%) experienced adverse events than those who received standard of care (22.6%).
- QT prolongation was more common in patients who received hydroxychloroquine plus azithromycin or hydroxychloroquine alone than in patients who received standard of care alone, but fewer patients in the standard of care alone group had serial electrocardiographic studies performed during the follow-up period.

Limitations

- The study was not blinded.
- The follow-up period was restricted to 15 days.

Interpretation

Neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Randomized Controlled Trial of Hydroxychloroquine Versus Standard of Care for Mild or Moderate COVID-19

This multicenter, randomized, open-label trial compared hydroxychloroquine 1,200 mg once daily for 3 days followed by hydroxychloroquine 800 mg once daily for the rest of the treatment duration (which was 2 weeks for patients with mild or moderate COVID-19 [99% of the patients] and 3 weeks for two patients with severe disease) to standard of care.[3]

Results

- Each study arm enrolled 75 patients. Patients were randomized at a mean of 16.6 days after symptom onset.
- The hydroxychloroquine arm and the standard of care arm had similar negative polymerase chain reaction (PCR) conversion rates within 28 days (85.4% of participants vs. 81.3% of participants) and similar times to negative PCR conversion (median of 8 days vs. 7 days).
- There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.

Limitations

- It is unclear how the overall rate of symptom alleviation was calculated.
- The study did not reach the target sample size.

Interpretation

This study demonstrated no difference in the rate of viral clearance between hydroxychloroquine and standard of care.

High-Dose Chloroquine Versus Low-Dose Chloroquine

A randomized, double-blind, Phase 2b study compared two different chloroquine regimens, chloroquine 600 mg twice daily for 10 days (high dose) and chloroquine 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected cases of severe COVID-19. All patients also received ceftriaxone plus azithromycin; 89.6% of patients received oseltamivir.[4]

The planned study sample size was 440 participants. The study was stopped by the study's data safety monitoring board after 81 patients were enrolled.

Results

- Forty-one patients were randomized into the high-dose arm and 40 patients were randomized into the low-dose arm.
- The overall fatality rate was 27.2%.
- Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%] vs. in six of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (OR 2.8; 95% CI, 0.9–8.5).
- Overall, QTcF >500 ms occurred more frequently in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients).
- Two patients in the high-dose arm experienced ventricular tachycardia before death.

Limitations

More older patients and more patients with a history of heart disease were randomized into the high-dose arm than into the low-dose arm.

Interpretation

Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose chloroquine (600 mg twice daily) is administered in combination with azithromycin and oseltamivir.

Randomized Placebo-Controlled Trial of Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19

This randomized, placebo-controlled trial in the United States and Canada enrolled participants with ≤4 days of symptoms that were compatible with COVID-19 and either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days. Participants were recruited through internet-based surveys. They were randomized to receive hydroxychloroquine (800 mg once, followed by 600 mg in 6–8 hours, and then 600 mg daily for 4 days) or placebo (with the same dosing frequency).

The planned primary endpoint was ordinal outcome by Day 14 in four categories: not hospitalized, hospitalized, intensive care unit (ICU) stay, or death. Due to lower than expected event rates, a new primary endpoint was defined: change in overall symptom severity over 14 days (assessed on a 10-point,

self-reported, visual analog scale). A longitudinal mixed model that was adjusted for baseline severity score was used for the anaylsis.[5]

Patient Characteristics

- Data were collected from 423 participants (212 in the hydroxychloroquine arm and 211 in the placebo arm) for the primary end point.
- Of the 423 participants, 241 were exposed to people with COVID-19 through their position as health care workers (57%), 106 were exposed through household contacts (25%), and 76 had other types of exposure (18%).
- The median age was 40 years, and 56% of patients were women. Only 3% of patients were Black. Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions.
- Fifty-six percent of patients were enrolled on Day 1 of symptom onset.
- In this study, 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact.

Results

- Compared to the placebo recipients, hydroxychloroquine recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$).
- Ongoing symptoms were reported by 24% of those on hydroxychloroquine and 30% of those in the placebo group at Day 14 ($P = 0.21$).
- There was no difference in the incidence of hospitalization (four patients in the hydroxychloroquine group vs. 10 patients in the placebo group). Two of the 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19.
- A higher percentage of patients who received hydroxychloroquine experienced adverse events (mostly gastrointestinal) than patients who received placebo (43% vs. 22%; $P < 0.001$).

Limitations

- This study enrolled a highly heterogenous participant population. Only 227 of the 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2.
- Changing the primary endpoint during the study without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms.
- This study used surveys for screening, symptom assessment, and adherence reporting.
- The visual analog scale has not been commonly used, and its ability to assess acute viral respiratory infections in clinical trials has not been validated.

Interpretation

The study has some limitations, and it did not find evidence that early administration of hydroxychloroquine reduced symptom severity in patients with mild COVID-19.

Open-Label Randomized Controlled Trial of Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19

This open-label randomized controlled trial in Spain enrolled nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection and <5 days of mild COVID-19 symptoms. Participants were mostly

health care workers. They were randomized to receive hydroxychloroquine (800 mg on Day 1, followed by 400 mg once daily for 6 days) or no antiviral treatment (control group). The primary endpoint was reduction in SARS-CoV-2 viral load, which was assessed using nasopharyngeal swabs on Days 3 and 7. Secondary endpoints were disease progression up to Day 28 and time to complete resolution of symptoms.[6]

Patient Characteristics

- Of 353 participants who were randomized into the hydroxychloroquine group or the control group, 60 were excluded from the intention to treat analysis because of negative baseline reverse transcription-PCR (RT-PCR), missing RT-PCR at all follow-up visits, or consent withdrawal.
- The intention to treat analysis included 293 patients (157 in the control group and 139 in the hydroxychloroquine group). Mean age was 41.6 years, and 67% of patients were women.
- The majority of patients were healthcare workers (87%), and 53% reported chronic health conditions.
- The median time from symptom onset to enrollment was 3 days (IQR 2–4 days). The most commonly reported COVID-19 symptoms were fever, cough, and sudden olfactory loss.

Results

- There was no significant difference in viral load reduction between the control group and hydroxychloroquine group at Day 3 (-1.41 vs. -1.41 $\log_{10}$ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 $\log_{10}$ copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29).
- There was no difference in the risk of hospitalization between the two groups: 7.1% vs. 5.9% (risk ratio 0.75; 95% CI, 0.32–1.77).
- There was no difference in the median time from randomization to the resolution of COVID-19 symptoms between the two groups (12.0 days in the control arm vs. 10.0 days in the hydroxychloroquine arm; $P = 0.38$).
- A higher percentage of participants in the hydroxychloroquine arm than in the control arm experienced adverse events during the 28-day follow-up period (72% vs. 9%). The most common adverse events were gastrointestinal disorders and "nervous system disorders."
- Serious adverse events were reported in 12 patients in the control group and in eight patients in the hydroxychloroquine group. The serious adverse events that occurred among the hydroxychloroquine patients were not deemed to be related to the drug.

Limitations

- This was an open-label, non-placebo-controlled trial. The study design allowed for the possibility of drop-outs in the control arm and over-reporting of adverse events in the hydroxychloroquine arm.
- There was a change in the intervention during the study; the authors initially planned to include a combination of hydroxychloroquine and darunavir/cobicistat.
- The majority of the participants were relatively young health care workers.

Interpretation

Early administration of hydroxychloroquine to patients with mild COVID-19 disease did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Observational Studies

New York Department of Health Study on Hydroxychloroquine With or Without Azithromycin

A retrospective, multicenter, observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into four treatment groups: hydroxychloroquine plus azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an electrocardiogram.[7]

Results

- Patients in the three treatment groups had more severe disease at baseline than those who received neither drug.
- In adjusted analyses, patients who received one of the three treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.
- Patients who received hydroxychloroquine plus azithromycin had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).

Limitations

Despite the large size of this study, it has the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

Despite the limitations discussed above, these findings suggest that although hydroxychloroquine and azithromycin are not associated with an increased risk of in-hospital death, the combination of hydroxychloroquine and azithromycin may be associated with an increased risk of cardiac arrest.

Observational Study of Hydroxychloroquine at a Large Medical Center in New York City

This observational study evaluated 1,376 consecutive adults hospitalized with COVID-19. The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received hydroxychloroquine at baseline or during follow-up. Patients who received hydroxychloroquine were prescribed a twice-daily dose of hydroxychloroquine 600 mg on the first day followed by 400 mg daily for 4 additional days; this was based on a clinical guidance protocol for the hospital.[8]

Results

- In this study, 811 patients (58.9%) received hydroxychloroquine and 565 (41.1%) did not.
- Hydroxychloroquine recipients were more severely ill at baseline than those who did not receive hydroxychloroquine.
- Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that hydroxychloroquine use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32).
- There was also no association between concomitant use of azithromycin and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).

Limitations

Despite the large size of this study, it has the inherent limitations of an observational study. These

include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

The use of hydroxychloroquine for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Observational Cohort of Hydroxychloroquine Versus No Hydroxychloroquine

This retrospective observational cohort study analyzed data for adult patients who were hospitalized for severe COVID-19 pneumonia at four French tertiary care centers. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization.[9]

Results

- Of the 181 patients who were eligible for the analysis, 84 participants received hydroxychloroquine within 48 hours, eight received hydroxychloroquine beyond 48 hours, and 89 did not receive hydroxychloroquine.
- In the hydroxychloroquine group, 18% of the patients received concomitant azithromycin.
- In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the hydroxychloroquine group (76% of participants) and the non-hydroxychloroquine group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival rate and survival rate without acute respiratory distress syndrome at Day 21.

Limitations

This was a retrospective, nonrandomized study.

Interpretation

In this retrospective study, there was no difference in the rates of clinically important outcomes between patients who received hydroxychloroquine within 48 hours of hospital admission and those who did not.

Retrospective Cohort Study that Compared Hydroxychloroquine to No Hydroxychloroquine in a Health Care System in Detroit, Michigan

A comparative, retrospective cohort study assessed the outcomes for all consecutive patients who were hospitalized for COVID-19 (which was defined as a positive SARS-CoV-2 PCR from a nasopharyngeal sample) from March 10 to May 2, 2020, in the Henry Ford Health System in Michigan.[10]

The primary outcome was in-hospital mortality. The study compared outcomes for patients who received hydroxychloroquine alone, hydroxychloroquine plus azithromycin, azithromycin alone, or neither drug.

An interdisciplinary task force of the health system established a COVID-19 treatment protocol that incorporated the use of hydroxychloroquine alone or in combination with azithromycin. The hydroxychloroquine dose was 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days. If azithromycin was used, the dose was azithromycin 500 mg for 1 day, then 250 mg daily for 4 days. The combination of hydroxychloroquine and azithromycin was reserved for patients with severe COVID-19 and minimal cardiac risks. The clinical treatment protocol allowed for the use of tocilizumab and corticosteroids in some patients; however, the criteria for their use were not specified in the report.

Study Population

- The analysis included 2,541 consecutive patients.
- The median patient age was 64 years (IQR 53–76 years); 51% of patients were men, 56% were African American, and 52% had a BMI ≥30.
- The median time to follow-up was 28.5 days (IQR 3–53 days).
- The modified sequential organ failure assessment (mSOFA) score was not available for 25% of patients.
- Corticosteroids were given to 79% of patients in the hydroxychloroquine alone group, 74% of patients in the hydroxychloroquine plus azithromycin group, and 35.7% of those on neither drug.

Mortality

- Overall, crude mortality was 18.1%. When broken down by the different groups, the mortality was 13.5% in hydroxychloroquine alone group, 20.1% in the hydroxychloroquine plus azithromycin group, 22.4% in the azithromycin alone group, and 26.4% in the group that received neither drug ($P < 0.001$).
- Mortality HRs were analyzed using a multivariable Cox regression model; the group that received neither drug was used as the reference. Hydroxychloroquine alone decreased the mortality HR by 66% ($P < 0.001$). Hydroxychloroquine plus azithromycin decreased the mortality HR by 71% ($P < 0.001$).
- Other predictors of mortality were age ≥65 years (HR 2.6; 95% CI, 1.9–3.3); White race (HR 1.7; 95% CI, 1.4–2.1); chronic kidney disease (HR 1.7; 95% CI, 1.4–2.1); reduced O_2 saturation level on admission (HR 1.6; 95% CI, 1.1–2.2); and ventilator use at admission (HR 2.2; 95% CI, 1.4–3.0).
- A propensity-matched Cox regression result suggested a mortality HR of 0.487 for patients who received hydroxychloroquine (95% CI, 0.285–0.832, $P = 0.009$).

Limitations

- This retrospective observational study evaluated one health care system with an institutional protocol for hydroxychloroquine and azithromycin use.
- Because the study was not randomized and not blinded, there is a possibility of residual confounding
- There was a lower rate of ICU admission among patients who did not receive hydroxychloroquine, which suggests that this group may have received less-aggressive care.
- A substantially higher percentage of patients in the hydroxychloroquine arms also received corticosteroids compared to the control arm (77.1% vs. 35.7%). Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit (see Corticosteroids), it is possible that the findings were confounded by this imbalance in corticosteroid use.[11]

Interpretation

This retrospective, propensity-matched cohort study reported a mortality benefit in hospitalized patients with COVID-19 who received either hydroxychloroquine alone or hydroxychloroquine plus azithromycin compared to receiving neither drug. However, there were substantial imbalances in corticosteroid use between the groups, which may have affected mortality. Moreover, because the study was retrospective and observational, it cannot control for other and unknown confounders.

Other Reviewed Studies

The COVID-19 Treatment Guidelines Panel (the Panel) has reviewed other clinical studies of hydroxychloroquine with or without azithromycin and studies of chloroquine for the treatment of COVID-19.[12-22] These studies have limitations (e.g., the potential for residual confounding, small sample sizes, incomplete reporting, a lack of comparison groups) that make them less definitive and informative than large randomized clinical trials. The Panel's summaries and interpretations of some of those studies are available in the archived versions of the COVID-19 Treatment Guidelines.

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Ivermectin

Last Updated: August 27, 2020

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.[1] It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock.[2] For these indications, ivermectin has been widely used and has demonstrated an excellent safety profile.[1]

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host antiviral response.[3] Ivermectin is therefore a host-directed agent, which is likely the basis for its broad-spectrum activity *in vitro* against the viruses that cause dengue, Zika, HIV, and yellow fever.[3-6]

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures.[7] However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected *in vitro* would require administration of doses up to 100-fold higher than those approved for use in humans.[8,9] Even though ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 *in vitro*.[10,11]

Ivermectin is not approved for the treatment of any viral infection, including SARS-CoV-2 infection. The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans.

Clinical Data in Patients With COVID-19

The available clinical data on the use of ivermectin to treat COVID-19 are limited.

Retrospective Analysis of Using Ivermectin in Patients With COVID-19

This study has not been peer reviewed.

This retrospective analysis of consecutive patients with confirmed SARS-CoV-2 infection (27% with severe COVID-19) who were admitted to four Florida hospitals compared patients who received at least one dose of ivermectin (n = 173) to those who received "usual care" (n = 103). The primary outcome was all-cause, in-hospital mortality. The secondary outcomes included mortality in patients with severe disease (defined as "need for either FiO_2 ≥50% or noninvasive or invasive mechanical ventilation") and extubation rates in those who were mechanically ventilated.[12]

Results

- Ivermectin administration was reportedly consistent with hospital guidelines: a single dose

of 200 µg/kg, with repeat dosing on Day 7 if the patient was still hospitalized (13 patients received a second dose). Ninety percent of the ivermectin group and 97% of the usual care group received hydroxychloroquine (the majority received hydroxychloroquine in conjunction with azithromycin).

- All-cause mortality was lower among the patients in the ivermectin group than among patients in the usual care group (OR 0.27; $P = 0.03$). The mortality benefit appeared to be limited to the subgroup of patients with severe disease.
- There was no difference between the groups for the median length of hospital stay (7 days in both groups) or the proportion of mechanically ventilated patients who were successfully extubated (36% in the ivermectin group vs. 15% in the usual care group; $P = 0.07$).

Limitations

- This was a retrospective analysis.
- The study included little or no information on oxygen saturation or radiographic findings. It was also unclear whether therapeutic interventions other than hydroxychloroquine, such as remdesivir or dexamethasone, were used in the study.
- The timing of therapeutic interventions was not standardized; if the timing is not accounted for, it can bias the survival comparison.
- The analyses of the durations of ventilation and hospitalization do not appear to account for death as a competing risk.
- No virologic assessments were performed.

Interpretation

The limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using ivermectin to treat patients with COVID-19.

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: July 17, 2020

Lopinavir/ritonavir and darunavir/cobicistat have been studied in patients with COVID-19.

The replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.[1] Two proteases are responsible for this cleavage: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).

Lopinavir/ritonavir is an inhibitor of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) 3CLpro *in vitro*, and this protease appears to be highly conserved in SARS-CoV-2.[2,3] Although lopinavir/ritonavir has *in vitro* activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.[4] Lopinavir is excreted in the gastrointestinal tract; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[5]

Darunavir inhibits the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibits the PLpro enzyme. However, in an *in vitro* study, darunavir did not show activity against SARS-CoV-2.[6]

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** using **lopinavir/ritonavir (AI)** or other **HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in a clinical trial.

Rationale

The pharmacodynamics of lopinavir/ritonavir raise concerns about whether it is possible to achieve drug concentrations that can inhibit the SARS-CoV-2 proteases. In addition, lopinavir/ritonavir did not show efficacy in a moderately sized randomized controlled trial in patients with COVID-19.

Adverse Effects

The adverse effects for lopinavir/ritonavir include:

- Nausea, vomiting, diarrhea (common)
- QTc prolongation
- Hepatotoxicity

Drug-Drug Interactions

Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A. Coadministering lopinavir/ritonavir with medications that are metabolized by this enzyme may increase the concentrations of those medications, resulting in concentration-related toxicities. Please refer to the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* for a list of potential drug interactions.

Considerations in Pregnancy

- There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and the drug has a good safety profile.
- There is no evidence of human teratogenicity (a 1.5-fold increase in overall birth defects can be ruled out).
- Lopinavir has low placental transfer to the fetus. Please refer to the *Recommendations for the*

Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States for more information.

- Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and **is not recommended** for use during pregnancy. Please refer to the *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States* for more information.
- The use of once-daily dosing for lopinavir/ritonavir **is not recommended** during pregnancy.

Considerations in Children

- Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents.
- There are no data on the efficacy of using lopinavir/ritonavir to treat COVID-19 in pediatric patients.

Clinical Data for COVID-19

- The plasma drug concentrations achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.[7]
- A moderately sized randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[8]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[9]
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Lopinavir/Ritonavir: Selected Clinical Data for more information.

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Lopinavir/Ritonavir: Selected Clinical Data

Last Updated: July 17, 2020

The information presented in this section may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see *ClinicalTrials.gov* for more information on clinical trials that are evaluating lopinavir/ritonavir.

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care

In a clinical trial that randomized 199 patients to receive lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days or standard of care, patients who were randomized to the lopinavir/ritonavir arm did not have a shorter time to clinical improvement.[1]

Results

- There was a lower, but not statistically significant, mortality rate for the lopinavir/ritonavir group (19.2%) than for the standard of care group (25.0%), and a shorter median intensive care unit stay for those in the lopinavir/ritonavir group than for those in the standard of care group (6 days vs. 11 days; 95% CI, -9 to 0 days).
- There was no difference in the median duration of hospital stay and the median time to clearance of viral RNA from respiratory tract samples between the two arms.
- Nausea, vomiting, and diarrhea were all more frequent among patients in the lopinavir/ritonavir-treated group.

Limitations

- The study was not blinded, which may have affected the assessments of clinical improvement.
- The study was underpowered to show small effects.

Interpretation

A moderately sized, randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.

Lopinavir/Ritonavir Plus Interferon Beta-1b Plus Ribavirin in Patients with COVID-19

Also see Interferons for a description of this trial and its results.

An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included interferon beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of lopinavir/ritonavir 400 mg/100 mg every 12 hours alone.[2]

In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, interferon beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only one participant was mechanically ventilated.

Results

Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group.

Limitations

- Participants in both arms received lopinavir/ritonavir, so it is impossible to determine whether lopinavir/ritonavir contributed to the observed treatment effects. However, the possibility that lopinavir/ritonavir may have contributed to the effectiveness of the combination therapy also cannot be ruled out.
- The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset.
- Most participants in this study had mild illness, and only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States.

Interpretation

This study neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Lopinavir/Ritonavir Versus Umifenovir Versus Standard of Care

In a trial of 86 hospitalized patients with mild to moderate COVID-19, 34 patients were randomized to receive lopinavir/ritonavir, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received standard of care.[3]

Results (Comparison of Lopinavir/Ritonavir to Standard of Care)

- The time to a negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid pharyngeal swab was similar for patients who received lopinavir/ritonavir (mean duration 9.0 days; SD ± 5.0 days) and for those who received standard of care (mean duration 9.3 days; SD ± 5.2 days).
- Progression to severe illness occurred among six patients (18%) in the lopinavir/ritonavir arm and two patients (12%) who received standard of care.
- Two patients became critically ill; both were randomized to receive lopinavir/ritonavir.

Limitations

- The trial had a small sample size.
- The study was not blinded.
- The effectiveness of umifenovir in treating COVID-19 is unknown.

Interpretation

The small sample size of this trial limits its usefulness.

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

In a case series, eight patients with COVID-19 were treated with lopinavir 400 mg/ritonavir 100 mg orally twice daily and had plasma trough levels of lopinavir drawn and assayed by liquid chromatography-tandem mass spectrometry.[4]

Results

- The median plasma lopinavir concentration was 13.6 μg/mL.
- After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the *in vitro* half-maximal effective concentration (EC_{50}) for SARS-CoV-2.

Limitations

- Only the trough levels of lopinavir were quantified.
- The concentration of lopinavir required to effectively inhibit SARS-CoV-2 replication *in vivo* is currently unknown.

Interpretation

The plasma drug concentrations that were achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.

References

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Table 2. Characteristics of Antiviral Agents That Are Under Evaluation for the Treatment of COVID-19

Last Updated: October 9, 2020

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data from patients with COVID-19, when available.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs in patients with COVID-19 are not well defined; the validity of extrapolation between patient populations (i.e., FDA-approved use vs. COVID-19 use) is unknown, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table, because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine	**Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg:** • CQ 1 g PO once on Day 1, then CQ 500 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if CQ is given with QTc-prolonging drugs or if the	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of CQ with or without AZM for the treatment of COVID-19 in hospitalized patients **(AI)**. • In nonhospitalized patients, the Panel **recommends against** the use of CQ with or without AZM for the

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine, continued		• Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash • Given the risk of heart rhythm problems, the FDA cautions against using CQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	patient has underlying cardiac disease		treatment of COVID-19, except in a clinical trial **(AI)**. • The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. • Dose-dependent toxicity • A list of clinical trials is available here: Chloroquine
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:** • HCQ 800 mg PO once on Day 1, then HCQ 400 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis • Allergic reaction/rash • Given the risk of heart rhythm problems, the FDA cautions against using HCQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if HCQ is given with QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac disease	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of HCQ with or without AZM for the treatment of COVID-19 in hospitalized patients **(AI)**. • In nonhospitalized patients, the Panel r**ecommends against** the use of HCQ with or without AZM for the treatment of COVID-19, except in a clinical trial **(AI)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Lopinavir/Ritonavir	**Adults:** • LPV 400 mg/RTV 100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • LPV 300 mg/m^2 plus RTV 75 mg/m^2 (maximum: LPV 400 mg/RTV 100 mg per dose) PO twice daily for a total of 7 days	• Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Transaminase elevation • QTc interval prolongation and Torsades de Pointes have been reported. • PR interval prolongation	• HIV antigen/antibody testing at baseline • Serum transaminase levels • Consider monitoring ECG when LPV/RTV is given with other QTc-prolonging medications.	**High Drug-Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > CYP2D6 substrate • Potent CYP3A4 and CYP2D6 inhibitor • Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19	• The Panel **recommends against** using LPV/RTV **(AI)** or other HIV PIs **(AIII)** to treat COVID-19, except in a clinical trial. • Liquid formulation is commercially available. Crushing LPV/RTV tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[2] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir **Note:** RDV is not approved by the FDA; however, it is available through an EUA,[a] a clinical trial, or the manufacturer's emergency access program.	**In Patients Who Are Participating in Clinical Trials:** • Dose according to the clinical trial protocol. **Panel's Recommendations for Adult and Pediatric Patients Weighing ≥40 kg** *For Patients With Severe COVID-19 Who Are Not Intubated:* • RDV 200 mg IV over 30–120 minutes for 1 dose, followed by RDV 100 mg IV on Day 2 through Day 5 **(AI)**.	• Transient elevations in ALT or AST levels (Grade 1 or 2), typically after multiple days of therapy[3] • Mild, reversible PT prolongation without INR change or hepatic effects[3] • Drug vehicle is SBECD, which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment.	• Monitor for infusion reactions. • Renal and hepatic function • **Do not administer** RDV if eGFR is <30 mL/min (or if patient is receiving dialysis), or if ALT or AST level is >5 times ULN	• Clinical studies of drug-drug interactions for RDV have not been conducted. • RDV levels are unlikely to be substantially altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters.	**Recommendation for Prioritizing Limited Supplies of RDV:** • Because RDV supplies are limited, the Panel recommends prioritizing RDV for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO **(BI)**.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued	*For Mechanically Ventilated Patients, Patients on ECMO, and Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:* • There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, and patients who have not shown adequate improvement after 5 days of therapy. Some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **Note:** The EUA recommends 10-day therapy for patients on mechanical ventilation or ECMO. **Suggested Dose in EUA[a] for Pediatric Patients Weighing 3.5 to <40 kg** *For Patients Who Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 10 *For Patients Who Do Not Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 5. If there is no clinical improvement, treatment may be extended for up to 5 additional days (for a total treatment duration of 10 days).	• Gastrointestinal symptoms (e.g., nausea, vomiting)		• RDV may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. • Strong induction may modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. Based on information provided by Gilead (written communication, July 2020), the use of RDV with strong inducers (e.g., rifampin) **is not recommended**. • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone. • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.	**Recommendation for Patients with Mild or Moderate COVID-19:** • There are insufficient data for the Panel to recommend either for or against the use of RDV in patients with mild or moderate COVID-19. **Recommendations for Patients With COVID-19 Who Require Supplemental Oxygen** *For Patients Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO:* • The Panel recommends using RDV for 5 days or until hospital discharge, whichever comes first **(AI)**. • If a patient who is on supplemental oxygen while receiving RDV progresses to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, the course of RDV should be completed. *For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO:* • Because there is uncertainty regarding whether starting RDV

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued					confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting RDV. **Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy:** • There are insufficient data on the optimal duration of RDV therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **Availability:** • RDV is available through an EUA[a] for the treatment of hospitalized adults and children with severe COVID-19. • RDV is also available for other patient populations through expanded access and compassionate use programs. • A list of clinical trials is available here: Remdesivir

[a] The FDA EUA permits the emergency use of the investigational product RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized adults and children.

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; AV = atrioventricular; AZM = azithromycin; CBC = complete blood count; CQ = chloroquine; CYP = cytochrome P; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LPV = lopinavir; LPV/RTV = lopinavir/ritonavir; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PI = protease inhibitor; PMA = postmenstrual age; PO = orally; PT = prothrombin time; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether-beta-cyclodextrin sodium; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCr = serum creatinine; UGT = uridine diphosphate glucuronosyltransferase; ULN = upper limit of normal

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