7: Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Remdesivir is the only Food and Drug Administration-approved drug 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 these antiviral agents, see Table 2d.

Remdesivir

- See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone.

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 **(AIIa)**.
- 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** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients **(AIII)**.

Ivermectin

- There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = 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 to 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 antiviral medications 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 COVID-19 Treatment Guidelines 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

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus Disease 2019 (COVID-19): a review. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32282022.
2. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32362390.

Remdesivir

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Remdesivir is an intravenous 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; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2]

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.

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. See Remdesivir: Selected Clinical Data for more information.

The safety and efficacy of combination therapy of remdesivir with corticosteroids have not been rigorously studied in clinical trials; however, there are theoretical reasons that the combination therapy may be beneficial in some patients with severe COVID-19. For the Panel's recommendations on using remdesivir with or without dexamethasone in certain hospitalized patients, see Therapeutic Management of Patients with COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time, and hypersensitivity reactions.

Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment as clinically indicated. Remdesivir may need to be discontinued if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed.[3]

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an estimated glomerular filtration rate (eGFR) of <50 mL/minute were excluded from some clinical trials; other trials had an eGFR cutoff of <30 mL/minute. Remdesivir **is not recommended** for patients with eGFR <30 mL/minute. Renal function should be monitored in patients before and during remdesivir treatment as clinically indicated.[3]

Clinical drug-drug interaction studies of remdesivir have not been conducted. In vitro, remdesivir is a substrate of cytochrome P450 (CYP) 3A4 and of the drug transporters organic anion-transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[3]

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**.[3] Remdesivir is not expected to have any significant interactions with oseltamivir or baloxavir, according to information provided by Gilead Sciences (written communications, August and September 2020).

See Table 2d: Characteristics of Antiviral Agents That Are Approved or Under Evaluation for Treatment of COVID-19 for more information.

Considerations in Pregnancy

- Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of use in pregnant patients through the remdesivir compassionate use program are reassuring.
- Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events.[4]
- Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

Considerations in Children

- The safety and effectiveness of remdesivir for the treatment of COVID-19 have not been evaluated in pediatric patients aged <12 years or weighing <40 kg.
- Remdesivir is available through an FDA EUA for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.
- A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier NCT04431453).

Clinical Trials

Several clinical trials that are evaluating remdesivir for the treatment of COVID-19 are currently underway or in development. Please see *ClinicalTrials.gov* for the latest information.

References

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Table 2a. Remdesivir: Selected Clinical Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for RDV. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)[1]			

Multinational, placebo-controlled, double-blind RCT in hospitalized patients (n = 1,062)	**Key Inclusion Criteria:**
	• Aged ≥18 years
	• Laboratory-confirmed SARS-CoV-2 infection
	• At least 1 of the following conditions:
	  • Pulmonary infiltrates, as determined by radiographic imaging
	  • SpO_2 ≤94% on room air
	  • Required supplemental oxygen
	  • Required mechanical ventilation
	  • Required ECMO
	Key Exclusion Criteria:
	• ALT or AST >5 times ULN
	• eGFR <30 mL/min
	• Pregnancy or breastfeeding
	Interventions:
	• IV RDV 200 mg on Day 1, then 100 mg daily for up to 9 more days
	• Placebo for 10 days
	Primary Endpoint:
	• Time to clinical recovery
	Ordinal Scale Definitions:
	1. Not hospitalized, no limitations
	2. Not hospitalized, with limitations
	3. Hospitalized, no active medical problems
		Number of Participants:
		• RDV (n = 541) and placebo (n = 521)
		Participant Characteristics:
		• Median time from symptom onset to randomization was 9 days (IQR 6–12 days).
		Outcomes
		Overall Results:
		• RDV reduced time to recovery compared to placebo (10 days vs. 15 days; RRR 1.29; 95% CI, 1.12–1.49; $P < 0.001$).
		• Clinical improvement based on ordinal scale was higher at Day 15 in RDV arm (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$).
		• No statistically significant difference in mortality by Day 29 between RDV and placebo arms (HR 0.73; 95% CI, 0.52–1.03; $P = 0.07$).
		• Benefit of RDV was greatest in patients randomized during the first 10 days after symptom onset.
		Results by Disease Severity at Enrollment:
		• No difference in median time to recovery between arms among patients who had mild to moderate disease at enrollment.
		• Benefit of RDV for reducing time to recovery was clearest in patients who required supplemental oxygenation at enrollment (n = 435; RRR 1.45; 95% CI, 1.18–1.79), and RDV appeared to confer
			Limitations:
			• Wide range of disease severity; study was not powered to detect differences within subgroups
			• Powered to detect differences in clinical improvement, not mortality
			• No data collected on longer-term morbidity
			Interpretation:
			• In patients with severe COVID-19, RDV reduced time to clinical recovery.
			• Benefit of RDV was most apparent in hospitalized patients on supplemental oxygen.
			• No observed benefit in those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups.
			• No observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)[1], continued			
	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 ECMO 8. Death	a survival benefit in this subgroup (HR for death by Day 29 0.30; 95% CI, 0.14–0.64). • No observed difference in time to recovery between arms in patients on high-flow oxygen or noninvasive ventilation at enrollment (RRR 1.09; 95% CI, 0.76–1.57). No evidence that RDV affected mortality rate in this subgroup (HR 1.02; 95% CI, 0.54–1.91). • No observed difference in time to recovery between arms in patients on mechanical ventilation or ECMO at enrollment (RRR 0.98; 95% CI, 0.70–1.36). No evidence that RDV affected mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89). *Safety Results:* • Percentages of patients with SAEs were similar between arms (25% vs. 32%). • Transaminase elevations: 6% of RDV recipients, 10.7% of placebo recipients	
Remdesivir Versus Placebo for Severe COVID-19 in China[2]			
Multicenter, placebo-controlled, double-blind RCT in hospitalized patients with severe COVID-19 (n = 237)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • Time from symptom onset to randomization <12 days • SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg • Radiographically confirmed pneumonia **Key Exclusion Criteria:** • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding	**Number of Participants:** • ITT analysis: RDV (n = 158) and placebo (n = 78) • Study stopped before reaching target enrollment of 453 patients due to control of the COVID-19 outbreak in China. **Participant Characteristics:** • Median time from symptom onset to randomization: 9 days for RDV arm, 10 days for placebo arm • Receipt of corticosteroids: 65% of patients in RDV arm, 68% in placebo arm • Receipt of LPV/RTV: 28% of patients in RDV arm, 29% in placebo arm	**Limitations:** • Sample size did not have sufficient power to detect differences in clinical outcomes. • Use of concomitant medications (i.e., corticosteroids, LPV/RTV, IFNs) may have obscured effects of RDV. **Interpretation:** • No difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between RDV-treated and placebo-treated patients;

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Placebo for Severe COVID-19 in China[2], continued			
	Interventions: • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • Saline placebo for 10 days **Primary Endpoint:** • Time to clinical improvement, defined as improvement on an ordinal scale or being discharged alive from the hospital	• Receipt of IFN alfa-2b: 29% of patients in RDV arm, 38% in placebo arm **Outcomes:** • No difference in time to clinical improvement between RDV and placebo arms (median time 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen with RDV (median time 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • 28-day mortality was similar between arms (14% of patients in RDV arm, 13% in placebo arm). • No difference between arms in SARS-CoV-2 viral load at baseline, and rate of decline over time was similar. • Percentage of patients with AEs: 66% in RDV arm, 64% in placebo arm • Discontinuations due to AEs: 12% of patients in RDV arm, 5% in placebo arm	however, study was underpowered to detect differences in these outcomes between arms.
World Health Organization Solidarity Trial[3]			
International, open-label, adaptive RCT with multiple treatment arms that enrolled hospitalized patients with COVID-19 (n = 11,330). In 1 arm, patients received RDV.	**Key Inclusion Criteria:** • Aged ≥18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours • Physician reported no contraindications to study drugs **Interventions:** • IV RDV 200 mg on Day 0, then 100 mg daily on Days 1–9 • Local SOC	**Number of Participants:** • ITT analysis: RDV (n = 2,743) and SOC (n = 2,708) **Participant Characteristics:** • Percentage of patients aged 50–69 years: 47% in RDV arm, 48% in SOC arm • Percentage of patients aged ≥70 years: 18% in RDV arm, 17% in SOC arm • 67% of patients in both arms were on supplemental oxygen at entry. • 9% of patients in both arms were mechanically ventilated at entry.	**Limitations:** • Open-label study design limits the ability to assess time to recovery; clinicians and patients were aware of treatment assignment, so RDV may have been continued to complete the treatment course even if the patient had improved. • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge

Study Design	Methods	Results	Limitations and Interpretation
World Health Organization Solidarity Trial[3], continued			

	Primary Endpoint:
	• In-hospital mortality
	Secondary Endpoints:
	• Initiation of mechanical ventilation
	• Duration of hospitalization
		• Percentage of patients hospitalized for ≥2 days at entry: 40% in RDV arm, 39% in SOC arm
		• Percentages of patients with comorbid conditions were similar between RDV and SOC arms: diabetes (26% and 25%), heart disease (21% both groups), and chronic lung disease (6% and 5%).
		• 48% of patients in both arms received corticosteroids.
		Primary Outcomes:
		• In-hospital mortality: 301 deaths (11.0%) in RDV arm, 303 deaths (11.2%) in SOC arm
		• Rate ratios for in-hospital death:
		  • Overall: 0.95 (95% CI, 0.81–1.11)
		  • No mechanical ventilation at entry: 0.86 (99% CI, 0.67–1.11)
		  • Mechanical ventilation at entry: 1.20 (99% CI, 0.80–1.80)
		Secondary Outcomes:
		• Initiation of mechanical ventilation: 295 patients (10.8%) in RDV arm, 284 patients (10.5%) in SOC arm
			Interpretation:
			• RDV did not decrease in-hospital mortality in hospitalized patients when compared to local SOC.

Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19[4]			
Open-label randomized trial in hospitalized patients (n = 596)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Moderate pneumonia, defined as radiographic evidence of pulmonary infiltrates and SpO_2 >94% on room air **Key Exclusion Criteria:** • ALT or AST >5 times ULN • CrCl <50 mL/min	**Number of Participants:** • 584 patients began treatment: 10-day RDV (n = 193), 5-day RDV (n = 191), and SOC (n = 200) **Participant Characteristics:** • Demographic and baseline disease characteristics were similar across all arms. **Outcomes:** • 5-day RDV had significantly higher odds of better clinical status distribution on Day 11 than SOC (OR 1.65; 95% CI, 1.09–2.48; *P* = 0.02).	**Limitations:** • Open-label design may have affected decisions related to concomitant medication use and hospital discharge. • Greater proportion of patients in SOC arm received HCQ, LPV/RTV, or AZM, which may cause AEs and have not shown clinical benefits in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19[4], continued			
	Interventions: • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • Local SOC **Primary Endpoint:** • Clinical status on Day 11, as measured by a 7-point ordinal scale	• Clinical status distribution on Day 11 was not significantly different between the 10-day RDV and SOC arms ($P = 0.18$). • By Day 28, there were more hospital discharges among patients who received RDV (89% in 5-day arm and 90% in 10-day arm) than those who received SOC (83%). • Mortality was low in all arms (1% to 2%). • Percentages of patients with AEs in RDV arms vs. SOC arm: nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%)	• No data on time to return to activity for discharged patients **Interpretation:** • Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better outcomes than those who received SOC; however, difference between arms was of uncertain clinical importance.
Different Durations of Remdesivir Treatment in Hospitalized Patients[5]			
Manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized patients with COVID-19 (n = 402)	**Key Inclusion Criteria:** • Aged ≥12 years • Laboratory-confirmed SARS-CoV-2 infection • Radiographic evidence of pulmonary infiltrates • SpO_2 ≤94% on room air or receipt of supplemental oxygen **Key Exclusion Criteria:** • Receipt of mechanical ventilation or ECMO • Multiorgan failure • ALT or AST >5 times ULN • Estimated CrCl <50 mL/min **Interventions:** • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days **Primary Endpoint:** • Clinical status at Day 14, as measured by a 7-point ordinal scale	**Number of Participants:** • 397 participants began treatment: 5-day RDV (n = 200) and 10-day RDV (n = 197) **Participant Characteristics:** • At baseline, patients in 10-day arm had worse clinical status (based on ordinal scale distribution) than those in 5-day arm ($P = 0.02$) **Outcomes:** • After adjusting for imbalances in baseline clinical status, Day 14 distribution in clinical status on the ordinal scale was similar between arms ($P = 0.14$). • Time to achieve clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar between arms (10 days vs. 11 days). • Median durations of hospitalization among patients discharged on or before Day 14 were similar between 5-day (7 days; IQR 6–10 days) and 10-day arms (8 days; IQR 5–10 days). • Percentages of patients with SAEs: 35% in 10-day arm, 21% in 5-day arm	**Limitations:** • This was an open-label trial without a placebo control arm, so clinical benefit of RDV (compared with no RDV) could not be assessed. • There were baseline imbalances in clinical status of patients in the 5-day and 10-day arms. **Interpretation:** • In hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had a similar clinical benefit.

Study Design	Methods	Results	Limitations and Interpretation
Different Durations of Remdesivir Treatment in Hospitalized Patients[5], continued			
		• Discontinuations due to AEs: 4% of patients in 5-day arm, 10% in 10-day arm	

Key: AE = adverse effects; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CrCl = creatinine clearance; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; IFN = interferon; ITT = intention to treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; RCT = randomized controlled trial; RDV = remdesivir; RRR = recovery rate ratio; SAE = serious adverse effects; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO_2 = saturation of oxygen; ULN = upper limit of normal

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 **(AIIa)**.
- 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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Table 2b. Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

Last Updated: October 9, 2020

The information in this table 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 CQ, HCQ, and AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM and studies of CQ for the treatment of COVID-19.[1-11] These studies have limitations that make them less definitive and informative than the studies discussed here. The Panel's summaries and interpretations of some of those studies are available in the archived versions of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial[12]			
Open-label RCT with multiple arms, including a control arm; in 1 arm, hospitalized patients received HCQ (n = 11,197) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Patients with prolonged QTc intervals were excluded from HCQ arm. **Interventions:** • HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge • Usual SOC **Primary Endpoint:** • All-cause mortality at Day 28 after randomization	**Number of Participants:** • HCQ (n = 1,561) and SOC (n = 3,155) • Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ. **Participant Characteristics:** • Mean age was 65 years in both arms; 41% of patients were aged ≥70 years. • 90% of patients had laboratory-confirmed SARS-CoV-2 infection. • 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. • At randomization, 17% of patients were receiving invasive mechanical ventilation or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. • Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone.	**Limitations:** • Not blinded • Information on occurrence of new major cardiac arrythmia was not collected throughout the trial. **Interpretation:** • HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. • Patients who received HCQ 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 HCQ.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial[12], continued			
		Outcomes: • No significant difference in 28-day mortality between the 2 arms; 418 patients (26.8%) in HCQ arm and 788 patients (25.0%) in SOC arm had died by Day 28 (RR 1.09; 95% CI, 0.96–1.23; *P* = 0.18). • A similar 28-day mortality for HCQ 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. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ 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 HCQ arm and 1,357 patients (43.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention.	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[13]			
Open-label, 3-arm RCT in hospitalized patients (n = 667)	**Key Inclusion Criteria:** • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days	**Number of Participants:** • Modified ITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). **Participant Characteristics:** • Mean age was 50 years. • 58% of patients were men. • At baseline, 58.2% of patients were ordinal level 3; 41.8% were ordinal level 4. • Median time from symptom onset to randomization was 7 days.	**Limitations:** • Not blinded • Follow-up period was restricted to 15 days. **Interpretation:** • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[13], continued			
	Key Exclusion Criteria: • Need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask • History of ventricular tachycardia • QT interval ≥480 ms **Interventions:** • HCQ 400 mg twice daily for 7 days plus SOC • HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC • SOC alone **Primary Endpoint:** • Clinical status at Day 15, as assessed by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection **Ordinal Scale Definitions:** 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, not on oxygen 4. Hospitalized, on oxygen 5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation 6. Hospitalized, on mechanical ventilation 7. Death	• 23.3% to 23.9% of patients received oseltamivir. **Outcomes:** • No significant difference between the odds of worse clinical status at Day 15 for patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$). • No significant differences in secondary outcomes of the 3 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 in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). • QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period.	

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine Versus Standard of Care for Mild or Moderate COVID-19[14]			
Multicenter, randomized, open-label trial (n = 150)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Severe conditions, including heart, liver, or kidney disease • Inability to take oral medications • Pregnancy or breastfeeding **Interventions:** • HCQ 1,200 mg once daily for 3 days, then HCQ 800 mg once daily for 2 weeks (in patients with mild or moderate COVID-19) or 3 weeks (in patients with severe disease) • SOC **Primary Endpoint:** • Negative conversion of SARS-CoV-2 by Day 28	**Number of Participants:** • HCQ (n = 75) and SOC (n = 75) **Participant Characteristics:** • Patients were randomized at a mean of 16.6 days after symptom onset. • 99% of patients had mild or moderate COVID-19. **Outcomes:** • HCQ arm and SOC arm had similar negative 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). • No difference in the probability of symptom alleviation between the arms in the ITT analysis.	**Limitations:** • Unclear how the overall rate of symptom alleviation was calculated • Study did not reach target sample size. **Interpretation:** • This study demonstrated no difference in the rate of viral clearance between HCQ and SOC.
High-Dose Chloroquine Versus Low-Dose Chloroquine[15]			

Randomized, double-blind, Phase 2b study in hospitalized adults (n = 81)	**Key Inclusion Criteria:**
	• Aged ≥18 years
	• Clinically suspected COVID-19
	• At least 1 of the following conditions:
	  • Respiratory rate >24 rpm
	  • Heart rate >125 bpm
	  • SpO_2 <90% on room air
	  • Shock
		Number of Participants:
		• High-dose CQ (n = 41) and low-dose CQ (n = 40)
		• Planned study sample size was 440 participants, but study was stopped by the study's DSMB.
		Participant Characteristics:
		• All patients also received ceftriaxone plus AZM.
		• 89.6% of patients received oseltamivir.
			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 CQ is administered in combination with AZM and oseltamivir.

Study Design	Methods	Results	Limitations and Interpretation
High-Dose Chloroquine Versus Low-Dose Chloroquine[15], continued			
	Interventions: • CQ 600 mg twice daily for 10 days (high dose) • CQ 450 mg twice daily for 1 day, then CQ 450 mg for 4 days (low dose) **Primary Endpoint:** • Mortality by Day 28	**Outcomes:** • Overall fatality rate was 27.2%. • Mortality by Day 13 was higher in high-dose arm than in low-dose arm (death occurred in 16 of 41 patients [39%] vs. in 6 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 high-dose arm (18.9% of patients) than in low-dose arm (11.1%). • In the high-dose arm, 2 patients experienced ventricular tachycardia before death.	
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19[16]			
Randomized, placebo-controlled trial in the United States and Canada (n = 491)	**Key Inclusion Criteria:** • ≤4 days of symptoms that were compatible with COVID-19 • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days **Key Exclusion Criteria:** • Aged <18 years • Hospitalized • Receipt of certain medications **Interventions:** • HCQ 800 mg once, then HCQ 600 mg in 6 to 8 hours, then HCQ 600 mg once daily for 4 days • Placebo	**Number of Participants:** • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) **Participant Characteristics:** • 241 patients 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%). • Median age was 40 years. • 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. • 56% of patients were enrolled on Day 1 of symptom onset. • 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact.	**Limitations:** • This study enrolled a highly heterogenous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint 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. • Visual analog scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19[16], continued			
	Primary Endpoints: • Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. • Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, assessed on a 10-point, self-reported, visual analog scale	**Outcomes:** • Compared to the placebo recipients, HCQ 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 in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). • No difference in the incidence of hospitalization (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19. • A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$).	**Interpretation:** • The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19[17]			
Open-label RCT in Spain (n = 353)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • <5 days of mild COVID-19 symptoms **Key Exclusion Criteria:** • Moderate to severe COVID-19 • Severe liver or renal disease • History of cardiac arrhythmia • QT prolongation **Interventions:** • HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days • No antiviral treatment	**Number of Participants:** • ITT analysis: HCQ (n = 136) and control (n = 157) • 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. **Participant Characteristics:** • Mean age was 41.6 years. • 67% of patients were woman. • Majority of patients were health care workers (87%). • 53% of patients reported chronic health conditions. • Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). • Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss.	**Limitations:** • Open-label, non-placebo-controlled trial • Study design allowed for the possibility of drop-outs in control arm and over-reporting of AEs in HCQ arm. • The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. • The majority of the participants were relatively young health care workers. **Interpretation:** • Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19[17], continued			
	Primary Endpoint: • Reduction in SARS-CoV-2 viral load, assessed using nasopharyngeal swabs on Days 3 and 7 **Secondary Endpoints:** • Disease progression up to Day 28 • Time to complete resolution of symptoms	**Outcomes:** • No significant difference in viral load reduction between control arm and HCQ arm 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). • No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77). • No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; $P = 0.38$). • A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and "nervous system disorders." • SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in HCQ arm were not deemed to be related to the drug.	
Observational Study on Hydroxychloroquine With or Without Azithromycin[18]			
Retrospective, multicenter, observational study in a random sample of inpatients with COVID-19 from the New York Department of Health (n = 1,438)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ plus AZM • HCQ alone • AZM alone • Neither drug **Primary Endpoint:** • In-hospital mortality	**Number of Participants:** • HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) **Participant Characteristics:** • Patients in the treatment arms had more severe disease at baseline than those who received neither drug. **Outcomes:** • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.	**Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin[18], continued			
	Secondary Endpoint: • Cardiac arrest and arrhythmia or QT prolongation on an ECG	• Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).	in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City[19]			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department **Interventions:** • HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days • No HCQ **Primary Endpoint:** • Time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death	**Number of Participants:** • Received HCQ (n = 811) and did not receive HCQ (n = 565) **Participant Characteristics:** • HCQ recipients were more severely ill at baseline than those who did not receive HCQ. **Outcomes:** • Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). • No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).	**Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France[20]			
Retrospective, observational cohort study in hospitalized adults with severe COVID-19 pneumonia at 4 tertiary care centers (n = 181)	**Key Inclusion Criteria:** • Aged 18 to 80 years • Laboratory-confirmed SARS-CoV-2 infection • Required supplemental oxygen **Key Exclusion Criteria:** • Started HCQ before hospital admission	**Number of Participants:** • Received HCQ within 48 hours (n = 84), received HCQ beyond 48 hours (n = 8), and did not receive HCQ (n = 89) **Participant Characteristics:** • In the HCQ arm, 18% of patients received concomitant AZM.	**Limitations:** • This was a retrospective, nonrandomized study. **Interpretation:** • There was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.

Study Design	Methods	Results	Limitations and Interpretation
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France[20], continued			
	• Received tocilizumab, LPV/RTV, or RDV within 48 hours of admission • Organ failure requiring immediate ICU admission • ARDS **Interventions:** • HCQ 600 mg once daily • No HCQ **Primary Endpoint:** • Survival without transfer to the ICU at Day 21 **Secondary Endpoints:** • Overall survival rate at Day 21 • Survival rate without ARDS at Day 21 • Weaning from oxygen by Day 21 • Discharge from hospital to home or rehabilitation by Day 21	**Outcomes:** • In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ arm (76% of participants) and the non-HCQ arm (75%). • No difference between the arms in the secondary outcomes of overall survival rate and survival rate without ARDS at Day 21.	
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan[21]			
Comparative, retrospective cohort study in hospitalized patients with COVID-19 in the Henry Ford Health System in Michigan (n = 2,541)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days • AZM 500 mg for 1 day, then 250 mg once daily for 4 days • HCQ plus AZM, at the above doses • Neither drug	**Number of Participants:** • HCQ alone (n = 1,202), AZM alone (n = 147), HCQ plus AZM (n = 783), and neither drug (n = 409) **Participant Characteristics:** • HCQ plus AZM was reserved for patients with severe COVID-19 and minimal cardiac risks. • 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. • Median time to follow-up was 28.5 days (IQR 3–53 days).	**Limitations:** • This study evaluated 1 health care system with an institutional protocol for HCQ and AZM 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 HCQ, which suggests that this group may have received less aggressive care.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan[21], continued			
	Primary Endpoint: • In-hospital mortality	• The mSOFA score was not available for 25% of patients. • Corticosteroids were given to 79% of patients in the HCQ alone arm, 74% of patients in the HCQ plus AZM arm, and 35.7% of those on neither drug. **Outcomes:** • Overall, crude mortality was 18.1%. When broken down by the different arms, mortality was 13.5% in HCQ alone arm, 20.1% in HCQ plus AZM arm, 22.4% in AZM alone arm, and 26.4% in the arm that received neither drug ($P < 0.001$). • Mortality HRs were analyzed using a multivariable Cox regression model; the arm that received neither drug was used as the reference. HCQ alone decreased the mortality HR by 66% ($P < 0.001$). HCQ plus AZM 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 HCQ (95% CI, 0.285–0.832, $P = 0.009$).	• Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit, it is possible that the findings were confounded by the imbalance in corticosteroid use among the arms. **Interpretation:** • This study reported a mortality benefit in hospitalized patients with COVID-19 who received either HCQ alone or HCQ plus AZM compared to patients who received neither drug. However, there were substantial imbalances in corticosteroid use among the arms, which may have affected mortality. • Because the study was retrospective and observational, it cannot control for confounders.

Key: AE = adverse effect; ARDS = acute respiratory distress syndrome; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; bpm = beats per minute; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; ITT = intention to treat; LPV/RTV = lopinavir/ritonavir; mSOFA = modified sequential organ failure assessment; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; QTcF = Fridericia's correction formula; RCT = randomized controlled trial; RDV = remdesivir; RR = rate ratio; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse effect; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care

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Ivermectin

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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 is generally well tolerated.[1,3] Ivermectin is not approved by the FDA for the treatment of any viral infection.

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

Reports from in vitro studies suggest that 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's antiviral response.[4,5] In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[6] Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.[4,7-9] Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[10-12]

Some observational cohorts and clinical trials have evaluated the use of ivermectin for the prevention and treatment of COVID-19. Data from some of these studies can be found in Table 2c.

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Rationale

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures.[13] 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.[14,15] 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.[16-19] Subcutaneous administration of ivermectin 400 µg/kg had no effect on SARS-CoV-2 viral loads in hamsters. However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.[20]

Since the last revision of this section of the Guidelines, the results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Some clinical studies showed no benefits or worsening of disease after ivermectin use,[21-24] whereas others reported shorter time to resolution of disease manifestations that were attributed to COVID-19,[25-28] greater reduction in inflammatory marker levels,[26,27] shorter time to viral clearance,[21,26] or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.[21,26,28]

However, most of these studies had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. These limitations include:

- The sample size of most of the trials was small.
- Various doses and schedules of ivermectin were used.
- Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.
- Patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids) in addition to ivermectin or the comparator drug. This confounded the assessment of the efficacy or safety of ivermectin.
- The severity of COVID-19 in the study participants was not always well described.
- The study outcome measures were not always clearly defined.

Table 2c includes summaries of key studies. Because most of these studies have significant limitations, the Panel cannot draw definitive conclusions on the clinical efficacy of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of ivermectin in the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.[29]
- Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.
- 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.
- Please see Table 2c for additional information.

Considerations in Pregnancy

In animal studies, ivermectin was shown to be teratogenic when given in doses that were maternotoxic. These results raise concerns about administering ivermectin to people who are in the early stages of pregnancy (prior to 10 weeks gestation).[30] A 2020 systematic review and meta-analysis reviewed the incidence of poor maternal and fetal outcomes after ivermectin was used for its antiparasitic properties during pregnancy. However, the study was unable to establish a causal relationship between ivermectin use and poor maternal or fetal outcomes due to the quality of evidence. There are numerous reports of inadvertent ivermectin use in early pregnancy without apparent adverse effects.[31-33] Therefore, there is insufficient evidence to establish the safety of using ivermectin in pregnant people, especially those in the later stages of pregnancy.

One study reported that the ivermectin concentrations secreted in breastmilk after a single oral dose were relatively low. No studies have evaluated the ivermectin concentrations in breastmilk in patients who received multiple doses.

Considerations in Children

Ivermectin is used in children weighing >15 kg for the treatment of helminthic infections, pediculosis, and scabies. The safety of using ivermectin in children weighing <15 kg has not been well established. Ivermectin is generally well tolerated in children, with a side effect profile similar to the one seen in adults. Currently, there are no available pediatric data from clinical trials to inform the use of ivermectin for the treatment or prevention of COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of ivermectin for the treatment of COVID-19 are currently underway or in development. Please see *ClinicalTrials.gov* for the latest information.

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Table 2c. Ivermectin: Selected Clinical Data

Last Updated: February 11, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IVM. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19[1]			
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	**Key Inclusion Criteria:** • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days **Key Exclusion Criteria:** • Chronic cardiac, renal, or liver disease **Interventions:** • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo **Primary Endpoints:** • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days	**Number of Participants:** • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) **Participant Characteristics:** • Mean age was 42 years. • 54% of participants were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. **Primary Outcomes:** • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms (P = 0.09, $P = 0.23$, and $P = 0.09$, respectively). **Other Outcomes:** • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization ($P = 0.93$). • No SAEs recorded.	**Limitations:** • Small sample size • Not clear whether both IVM and DOX placebos were used. • Patients with chronic diseases were excluded. • Disease appears to have been mild in all participants; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers are not presented but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. **Interpretation:** • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat). Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Outpatients With Mild COVID-19[2]			
Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)	**Key Inclusion Criteria:** • SARS-CoV-2 PCR positive • Mild disease **Key Exclusion Criteria:** • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy **Interventions:** • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment **Primary Endpoint:** • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic.	**Number of Participants:** • IVM (n = 25) and control (n = 25) **Participant Characteristics:** • Mean age was 40.6 years. • 62% of participants were male. • 40% of participants had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity. **Outcomes:** • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; $P = 0.500$). • AEs were attributed to IVM in 8 patients (32%).	**Limitations:** • Small sample size • Open-label study • Authors reported the proportions of participants with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms. • Study classified outcomes at Day 7 as "symptomatic" and "asymptomatic," but did not account for symptom worsening or improvement. **Interpretation:** • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19[3]			
RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions** *Group A:* • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days	**Number of Participants:** • Group A (n = 60) and Group B (n = 56) **Participant Characteristics:** • Mean age was 33.9 years. • 72% of participants were male. • 91 of 116 participants (78.5%) were symptomatic. **Outcomes:** • In Group A, PCR became negative in 60 of 60 patients (100%). Mean time to negative PCR result was 8.93 days (range 8–13 days).	**Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19[3], continued			
	Group B: • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days **Primary Endpoints:** • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms	• In Group B, PCR became negative in 54 of 56 patients (96.4%). Mean time to negative PCR result was 9.33 days (range 5–15 days). • Difference between groups in time from recovery to negative PCR result was not statistically significant ($P = 0.2314$). • In a subgroup analysis of patients who were symptomatic at baseline, the mean durations to negative PCR for Groups A and B were 9.06 days and 9.74 days, respectively ($P = 0.0714$). • In the subgroup analysis, the mean symptom recovery durations for Groups A and B were 5.93 days (range 5–10 days) and 6.99 days (range 4–12 days), respectively ($P = 0.071$). • Patients receiving IVM plus DOX had fewer AEs than those receiving HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis.	**Interpretation:** • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[4]			
A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia **Interventions:** • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care **Primary Endpoint:** • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment	**Number of Participants:** • IVM (n = 12) and placebo (n = 12) **Participant Characteristics:** • Mean age was 26 years (range 18–54 years). • 50% of participants were male. • All participants had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. **Outcomes:** • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); $P = 1.0$ for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion.	**Limitations:** • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. **Interpretation:** • Patients who received IVM showed no difference in viral clearance compared to those who received placebo.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[4], continued			
			• The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19[5]			
Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iran (n = 140) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Diagnosis by clinical, radiological, and PCR testing • Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. **Interventions:** • IVM 200 µg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). • Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. • All critically ill patients were assigned to receive IVM plus DOX.	**Number of Participants:** • IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) **Participant Characteristics:** • Median age was 50 years in IVM arm and 47 years in standard therapy arm. • 50% of patients were male in IVM arm and 53% were male in standard therapy arm. • In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. • In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. **Outcomes:** • Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. • Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) • 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$)	**Limitations:** • Not blinded • Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. • Relies heavily on post hoc subgroup comparisons. • Substantial imbalance in disease severity at baseline • Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. • Unclear how many patients required corticosteroids. **Interpretation:** • IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy and Safety of Ivermectin Versus Hydroxychloroquine for Treatment of COVID-19[6]			
Multicenter RCT that compared the use of IVM and HCQ in patients with mild, moderate, or severe COVID-19 in hospital settings (n = 400) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Positive RT-PCR result • Mild, moderate, or severe cases of COVID-19 **Key Exclusion Criteria:** • Contraindications for HCQ • Critical cases of COVID-19 • Chronic kidney, liver, or heart disease **Interventions** *All Patients:* • SOC, which included AZM 500 mg once daily for 6 days, vitamin C 1 gm once daily, zinc 50 mg once daily, lactoferrin 100 mg twice daily, acetylcysteine 200 mg 3 times daily, prophylactic or therapeutic anticoagulation if D-dimer >1,000, and paracetamol as needed. *Group 1 (Mild or Moderate) and Group 3 (Severe):* • IVM 400 µg/kg once daily for 4 days (maximum of IVM 24 mg per day) *Group 2 (Mild or Moderate) and Group 4 (Severe):* • HCQ 400 mg every 12 hours on Day 1, then HCQ 200 mg every 12 hours for 5 days **Primary Endpoints:** • Clinical laboratory improvement and/or 2 consecutive negative PCR results ≥48 hours apart • Length of hospital stay	**Number of Participants:** • All 4 arms (n = 100 in each arm) **Participant Characteristics:** • Mean age was 53.8–59.6 years. • 67% to 72% of patients were male. • Fatigue and dyspnea reported in 36% to 38% of patients with mild or moderate disease and 86% to 88% of those with severe disease. **Primary Outcomes:** • In those with mild or moderate disease, patients who received IVM had significant differences in improvement compared to those who received HCQ (99% vs. 74%), progression of disease (1% vs. 22%), death (0% vs. 4%), and mean number of hospital days (5±1 vs. 15±8) ($P <$ 0.001 for all parameters except death). • For those with severe disease, patients who received IVM had significant differences compared to those who received HCQ in improvement (94% vs. 50%), progression of disease (4% vs. 30%), death (2% vs. 20%), and mean number of hospital days (6±8 vs. 18±8) ($P < 0.001$ for all parameters). • For all patients, those treated with IVM had significant improvement in TLC, CRP, ferritin, D-dimer, and RT-PCR conversion days by Week 1 ($P < 0.001$) compared to those who received HCQ. • In addition to the markers listed above, patients with severe disease showed greater improvement in hemoglobin in IVM arm than in HCQ arm.	**Limitations:** • Unclear whether the study team and patients were blinded. • The role of SOC therapy in clinical and laboratory responses is unknown. • Cannot rule out potential harm from HCQ. It is unknown whether using AZM plus HCQ could have led to worse outcomes. • No SOC alone group • Laboratory results are only reported after 1 week of treatment. Length of follow up for clinical outcomes and mortality is unclear. **Interpretation:** • Compared to those who received HCQ, IVM recipients had improved inflammatory markers and time to RT-PCR conversion after 1 week. Improvement in clinical status and decreased mortality was also observed in the IVM arm.

Study Design	Methods	Results	Limitations and Interpretation
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19[7]			

Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 (n = 45)
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Laboratory-confirmed SARS-CoV-2 infection
	• Hospitalized with WHO Stage 3 to 5 COVID-19
	• ≤5 days of symptoms
	Key Exclusion Criteria:
	• Use of any agent with potential anti-SARS-CoV-2 activity or immunomodulators prior to enrollment
	• Poorly controlled comorbidities
	Interventions:
	• IVM 600 µg/kg once daily plus SOC for 5 days
	• SOC for 5 days
	Primary Endpoint:
	• VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5.
	PK Sampling:
	• Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination
		Number of Participants:
		• IVM (n = 30) and SOC (n = 15)
		• After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population.
		Participant Characteristics:
		• Mean age was 40.9 years ± 12.5 years.
		• 56% of patients were male.
		Primary Outcomes:
		• Nonstatistically significant difference in baseline VL between arms. The baseline median VL was 3.74 $\log_{10}$ copies/mL (range 2.8–5.79) in IVM arm and 5.59 $\log_{10}$ copies/mL in SOC arm ($P = 0.08$).
		• By Day 5, a similar magnitude of viral reduction was seen in both arms.
		Other Outcomes:
		• A significant positive correlation was found after analysis of mean plasma IVM concentration in relation to VL reduction. Participants with higher IVM concentrations had greater reductions in VL (r 0.44; $P < 0.04$). This correlation was stronger when reduction in VL was related to the IVM exposure corrected by baseline VL (r 0.60; $P < 0.004$).
		• Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and ≤160 ng/mL (median of 109 ng/mL).
		  • Median percentage of VL reduction by C_{max} concentration vs. control ($P = 0.0096$) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in ≤160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm.
		  • Median viral decay rate ($P = 0.041$) was 0.64 d^{-1} in >160 ng/mL group, 0.14 d^{-1} in ≤160 ng/mL group, and 0.13 d^{-1} in SOC arm.
		• Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild. No correlation was found between IVM concentration and the occurrence of AEs.
			Limitations:
			• Small sample size
			• No clinical response data reported.
			• The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary.
			Interpretation:
			• Concentration-dependent virologic response was seen using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once daily), with minimal associated toxicities.
			• The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19[8]			

Randomized, double-blind, placebo-controlled multicenter Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180)
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2
	Key Exclusion Criteria:
	• Severe immunosuppression, malignancy, or chronic kidney disease
	• Pregnancy
	Interventions:
	• HCQ 200 mg/kg twice daily alone as SOC (standard arm)
	• SOC plus 1 of the following:
	  • Placebo
	  • Single dose of IVM 200 µg/kg
	  • IVM 200 µg/kg on Days 1, 3, and 5
	  • Single dose of IVM 400 µg/kg
	  • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5
	Primary Endpoint:
	• Clinical recovery within 45 days of enrollment (defined as normal temp, respiratory rate, and SpO_2 >94% for 24 hours)
		Number of Participants:
		• All 6 arms (n = 30 in each arm)
		Participant Characteristics:
		• Average age was 56 years (range 45–67 years).
		• 50% of patients were male.
		• Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%)
		• Mean SpO_2 at baseline was 89%.
		Primary Outcomes:
		• Durations of hypoxemia (P = 0.025) and hospitalization (P = 0.006) were shorter in the IVM arms compared to placebo arm, and mortality was lower in the IVM arms (P = 0.001).
		• There was no difference in number of days of tachypnea (P = 0.584) or return to normal temperature (P = 0.102).
		• Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP.
		• Higher mortality was reported in standard and placebo arm than IVM arms.
			Limitations:
			• Small study
			• Power estimation is confusing.
			• Mortality was not listed as the primary or secondary outcome.
			• It is unclear whether IVM patients also received HCQ.
			• It is unclear whether the between-group comparisons are between combined IVM group and placebo plus SOC.
			• Participants were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons.
			• The post hoc grouping of randomized arms raises risk of false positive findings.
			Interpretation:
			• IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality.
			• The small size of the study, the unclear treatment arm assignments, and the lack of accounting of disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19[9]			
Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)	**Key Inclusion Criteria:** • Positive NP swab with SARS-CoV-2 RNA **Interventions:** • Single dose of IVM 200 µg/kg, repeated on Day 7 at the doctors' discretion; 90% percent of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. **Primary Endpoint:** • All-cause, in-hospital mortality	**Number of Participants:** • IVM (n = 173; 160 participants received a single dose, 13 participants received a second dose) and usual care (n = 103) **Participant Characteristics:** • Mean age was 60.2 years in IVM arm and 58.6 years in the usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. **Outcomes:** • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; *P* = 0.03); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; *P* = 0.07).	**Limitations:** • Not randomized • Little to no information on oxygen saturation or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. **Interpretation:** • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19[10]			

Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683)
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Symptomatic
	• Laboratory-confirmed SARS-CoV-2 infection
	• No life-threatening illness at admission
	Key Exclusion Criteria:
	• Required oxygen at admission
	• Use of tocilizumab, LPV/RTV, or RDV
	Interventions:
	• One of the following interventions administered within 48 hours of admission:
	  • HCQ or CQ alone
	  • IVM alone
	  • AZM alone
	  • HCQ or CQ plus AZM
	  • IVM plus AZM
	  • SOC (e.g., supportive care, antipyretics, hydration)
	Primary Endpoint:
	• All-cause mortality
	Secondary Endpoint:
	• All-cause mortality and/or transfer to ICU
		Number of Participants:
		• HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630)
		Participant Characteristics:
		• 63% of patients were male.
		• Mean age was 59.4 years (range 18–104 years).
		• All patients had mild or moderate disease.
		Outcomes:
		• Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow up.
		• IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25).
		• IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC.
		• HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC.
			Limitations:
			• Not randomized
			• Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript.
			• Dosing and timing of administration are unclear.
			Interpretation:
			• Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19[11]			
Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • "Free from any other serious pathological conditions" **Interventions:** • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC **Primary Outcome:** • Not specified	**Number of Participants:** • IVM (n = 115) and SOC (n = 133) **Participant Characteristics:** • Median age in IVM arm was 34 years; 70% of participants were male. • Median age in SOC arm was 35 years; 52% of participants were male. • All participants had mild or moderate disease. • 12% of participants had hypertension in both arms. • 17% of participants in IVM arm and 12% in SOC arm had diabetes mellitus. **Outcomes:** • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$)	**Limitations:** • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had SpO_2 <94% • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications **Interpretation:** • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality

Key: AE = adverse event; AZM = azithromycin; C_{max} = maximum concentration; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DOX = doxycycline; HCQ = hydroxychloroquine; ICU = intensive care unit; IVM = ivermectin; LDH = lactose dehydrogenase; LPV/RTV = lopinavir/ritonavir; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PK = pharmacokinetic; PO = orally; r = correlation coefficient; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; SpO_2 = oxygen saturation; TLC = total lymphocyte count; VL = viral load; WHO = World Health Organization; wHR = weighted hazard ratio

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: February 11, 2021

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 and darunavir/cobicistat have been studied in patients with COVID-19. The clinical trials discussed below have not demonstrated a clinical benefit for protease inhibitors in patients with COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients **(AIII)**.

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.[2,3] In addition, lopinavir/ritonavir did not show efficacy in two large randomized controlled trials in hospitalized patients with COVID-19.[4,5]

There is currently a lack of data on the use of lopinavir/ritonavir in nonhospitalized patients with COVID-19. However, the pharmacodynamic concerns and the lack of evidence for a clinical benefit among hospitalized patients with COVID-19 undermine confidence that lopinavir/ritonavir has a clinical benefit at any stage of SARS-CoV-2 infection.

Adverse Events

The adverse events 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 the risk of 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.

Summary of 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.[3]
- Lopinavir/ritonavir did not demonstrate a clinical benefit in hospitalized patients with COVID-19 during a large randomized trial in the United Kingdom.[4]
- In a large international randomized trial, lopinavir/ritonavir did not reduce the mortality rate among hospitalized patients with COVID-19.[5]
- A moderately sized randomized trial (n = 199) failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[6]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[7]
- 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.

Clinical Data for 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 lopinavir/ritonavir.

Lopinavir/Ritonavir in Hospitalized Patients With COVID-19: The RECOVERY Trial

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received lopinavir/ritonavir. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection.[4]

Patients were randomized into several parallel treatment arms; this included randomization in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours for 10 days or until hospital discharge. Patients who had severe hepatic insufficiency or who were receiving medications that had potentially serious or life-threatening interactions with lopinavir/ritonavir were excluded from randomization into either of these

arms. Mechanically ventilated patients were also underrepresented in this study because it was difficult to administer the oral tablet formulation of lopinavir/ritonavir to patients who were on mechanical ventilation. The primary outcome was all-cause mortality at Day 28 after randomization.

The lopinavir/ritonavir arm was discontinued on June 29, 2020, after the independent data monitoring committee concluded that the data showed no clinical benefit for lopinavir/ritonavir.

Patient Characteristics

- Of the 7,825 participants who were eligible to receive lopinavir/ritonavir, 1,616 were randomized to receive lopinavir/ritonavir and 3,424 were randomized to receive standard of care only. The remaining participants were randomized to other treatment arms in the study.
- In both the lopinavir/ritonavir arm and the standard of care arm, the mean age was 66 years; 44% of patients were aged ≥70 years.
- Test results for SARS-CoV-2 infection were positive for 88% of patients. The remaining 12% had a negative test result.
- Comorbidities were common; 57% of patients had at least one major comorbidity. Of those patients, 28% had diabetes mellitus, 26% had heart disease, and 24% had chronic lung disease.
- At randomization, 4% of patients were receiving invasive mechanical ventilation, 70% were receiving oxygen only (with or without noninvasive ventilation), and 26% were receiving neither.
- The percentages of patients who received azithromycin or another macrolide during the follow-up period were similar in both arms (23% in the lopinavir/ritonavir arm vs. 25% in the standard of care arm). In addition, 10% of patients in both arms received dexamethasone.

Results

- There was no significant difference in the primary outcome of 28-day mortality between the two arms; 374 patients (23%) in the lopinavir/ritonavir arm and 767 patients (22%) in the standard of care arm had died by Day 28 (rate ratio 1.03; 95% CI, 0.91–1.17; $P = 0.60$).
- A similar 28-day mortality was reported for patients who received lopinavir/ritonavir in an analysis that was restricted to the 4,423 participants who had positive SARS-CoV-2 test results (rate ratio 1.05; 95% CI, 0.92–1.19; $P = 0.49$).
- Patients in the lopinavir/ritonavir arm and patients in the standard of care arm had similar median times to discharge (11 days in both arms) and similar probabilities of being discharged alive within 28 days (69% vs. 70%).
- Among participants who were not on invasive mechanical ventilation at baseline, patients who received lopinavir/ritonavir and those who received standard of care only had similar risks of progression to intubation or death.
- Results were consistent across subgroups defined by age, sex, ethnicity, or respiratory support at baseline.

Limitations

- The study was not blinded.
- No laboratory or virologic data were collected.

Interpretation

Lopinavir/ritonavir did 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 received lopinavir/ritonavir and those who received standard of care only had similar median lengths of hospital stay. Among the patients who were not on invasive mechanical ventilation at

the time of randomization, those who received lopinavir/ritonavir were as likely to require intubation or die during hospitalization as those who received standard of care.

Lopinavir/Ritonavir in Hospitalized Patients with COVID-19: The Solidarity Trial

The Solidarity trial was an open-label, randomized controlled trial that enrolled hospitalized patients with COVID-19 in 405 hospitals across 30 countries. The study included multiple arms; in one arm, participants received lopinavir/ritonavir. The control group for this arm included people who were randomized at the same site and time who could have received lopinavir/ritonavir but received standard of care instead. Lopinavir 400 mg/ritonavir 100 mg was administered orally twice daily for 14 days or until hospital discharge. Only the oral tablet formulation of lopinavir/ritonavir was available, which precluded administration to those on mechanical ventilation. The primary outcome was in-hospital mortality.[5]

After the results of the RECOVERY trial prompted a review of the Solidarity data, the lopinavir/ritonavir arm ended enrollment on July 4, 2020. At that time, 1,411 patients had been randomized to receive lopinavir/ritonavir, and 1,380 patients received standard of care.

Patient Characteristics

- In both the lopinavir/ritonavir arm and the standard of care arm, 20% of the participants were aged ≥70 years and 37% were aged <50 years.
- Comorbidities were common. Diabetes mellitus was present in 24% of patients, heart disease in 21%, and chronic lung disease in 7%.
- At randomization, 8% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 53% were receiving oxygen only (with or without noninvasive ventilation), and 39% were receiving neither.
- Similar percentages of patients received corticosteroids in the lopinavir/ritonavir arm and the standard of care arm (23% vs. 24%). Other nonstudy treatments were administered less often, and the use of these treatments was balanced between arms.

Results

- There was no significant difference in in-hospital mortality between the two arms; 148 patients (9.7%) in the lopinavir/ritonavir arm and 146 patients (10.3%) in the standard of care arm had died by Day 28 (rate ratio 1.00; 95% CI, 0.79–1.25; $P = 0.97$).
- Progression to mechanical ventilation among those who were not ventilated at randomization occurred in 126 patients in the lopinavir/ritonavir arm and 121 patients in the standard of care arm.
- In-hospital mortality results appeared to be consistent across subgroups.

Limitations

- The study was not blinded.
- Those who were on mechanical ventilation were unable to receive lopinavir/ritonavir.
- The study includes no data on time to recovery.

Interpretation

Among hospitalized patients, lopinavir/ritonavir did not decrease in-hospital mortality or the number of patients who progressed to mechanical ventilation compared to standard of care.

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.[3]

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.

Other Reviewed Studies

The Panel has reviewed other clinical studies that evaluated the use of protease inhibitors for the treatment of COVID-19.[6,8,9] These studies have limitations that make them less definitive and informative than larger randomized clinical trials. The Panel's summaries and interpretations of some of these studies are available in the archived versions of the Guidelines.

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

Last Updated: February 11, 2021

- 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 on their use in 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.
- 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.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**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 • GI effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if CQ is given with QTc-prolonging drugs 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 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 treatment of COVID-19, except in a clinical trial **(AIIa)**. • The Panel **recommends against** the use of 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

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Panel's Recommendations, Comments, and Links to Clinical Trials**
Chloroquine, continued				
	• 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]			
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 • GI 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 **recommends against** the use of HCQ with or without AZM for the treatment of COVID-19, except in a clinical trial **(AIIa)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Ivermectin				
Adults: • The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg given as a single dose or as a once-daily dose for up to 5 days.	• Generally well tolerated • Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported with the use of IVM for the treatment of parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• There are insufficient data for the Panel to recommend either for or against the use of IVM for the treatment of COVID-19. • Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[2] • A list of clinical trials is available here: Ivermectin
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 dose LPV 400 mg/RTV 100 mg) PO twice daily for a total of 7 days	• GI 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** the use of LPV/RTV for the treatment of COVID-19 in hospitalized patients **(AI)**. • The Panel **recommends against** the use of LPV/RTV for the treatment of COVID-19 in nonhospitalized patients **(AIII)**. • Liquid formulation is commercially available. Crushing LPV/RTV tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[3] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir				
For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg)	• Nausea • ALT and AST elevations • Hypersensitivity	• Infusion reactions • Renal function, hepatic function,	• Clinical drug-drug interaction studies of RDV have not been conducted.	• See Therapeutic Management of Patients with COVID-19 for recommendations on using RDV with or without dexamethasone.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued				
For Patients Who Are Not Mechanically Ventilated and/or on ECMO: • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5 • In patients who have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days. *For Mechanically Ventilated Patients and/or Patients on ECMO:* • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10 **Suggested Dose in EUA[a] for Hospitalized Pediatric Patients Weighing 3.5 kg to <40 kg or Aged <12 Years and Weighing ≥3.5 kg** *For Patients Weighing 3.5 kg to <40 kg:* • RDV 5 mg/kg IV over 30–120 minutes on Day 1, followed by RDV 2.5 mg/kg once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days.	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD.	and prothrombin time should be monitored before and during treatment as clinically indicated. • **Not recommended** if eGFR is <30 mL/min • RDV may need to be discontinued if ALT levels increase to >10 times the ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.[4]	• In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[4] • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.[4] • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. **Availability:** • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUA[a] is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. • A list of clinical trials is available here: Remdesivir

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued				
• For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. *For Patients Aged <12 Years and Weighing ≥40 kg:* • Same dose as for adults and children aged ≥12 years and weighing >40 kg				

[a] The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.[5]

Key: AE = adverse event; 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; GI = gastrointestinal; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; IV = intravenous; IVM = ivermectin; LPV = lopinavir; LPV/RTV = lopinavir/ritonavir; MATE = multidrug and toxin extrusion protein; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PMA = postmenstrual age; PO = orally; RDV = remdesivir; RTV = ritonavir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SBECD = sulfobutylether-beta-cyclodextrin; SCr = serum creatinine; UGT = uridine diphosphate glucuronosyltransferase; ULN = upper limit of normal

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