# Table 2b. Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data

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The information in this table may include data from preprints or articles that have not been peer reviewed.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/or AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM, CQ, and AZM for the treatment of COVID-19.[1-19] 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 |
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| **Solidarity Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[20]** | | | |
| Open-label randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,330) | **Key Inclusion Criteria:**<br>• Aged ≥18 years<br>• Received a diagnosis of COVID-19<br>**Key Exclusion Criteria:**<br>• Already receiving study drug<br>• Expected to be transferred elsewhere within 72 hours<br>**Interventions:**<br>• HCQ plus local SOC. Patients received a loading dose of HCQ 800 mg PO at entry, then HCQ 800 mg PO 6 hours later followed by a daily dose of HCQ 400 mg PO twice daily for 10 days, starting 12 hours after the entry dose.<br>• Local SOC alone | **Number of Participants:**<br>• ITT analysis: HCQ (n = 947) and HCQ control (n = 906)<br>• Enrollment occurred between March 22 and October 4, 2020.<br>**Participant Characteristics:**<br>• 35% of patients enrolled in each arm were aged <50 years; 21% of patients were aged ≥70 years.<br>• 21% to 23% of patients had diabetes mellitus, 20% to 21% had heart disease, and 6.5% to 7% had chronic lung disease.<br>• At entry, 36% to 38% of patients were not on supplemental oxygen, 53% to 55% were receiving supplemental oxygen only, and 9% were receiving IMV.<br>• SOC included corticosteroids for 23% of patients in HCQ arm and 22% of patients in SOC only arm.<br>**Outcomes:**<br>• No significant difference in in-hospital mortality; 104 patients (10.2%) in HCQ arm and 84 patients (8.9%) in SOC arm died by Day 28 (rate ratio 1.19; 95% CI, 0.89–1.59; *P* = 0.23). | **Key Limitations:**<br>• Not blinded<br>• Disease severity varied widely among patients.<br>**Interpretation:**<br>• HCQ does not decrease in-hospital mortality in hospitalized patients with COVID-19 when compared to SOC.<br>• HCQ does not decrease the need for mechanical ventilation when compared to SOC.<br>• There was no evidence of harm in the HCQ arm. |

| Study Design | Methods | Results | Limitations and Interpretation |
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| **Solidarity Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[20]**, continued | | | |
| | **Primary Endpoint:**<br>• In-hospital mortality (i.e., death during the original hospitalization; follow-up ended at discharge from the hospital) | • Subgroup analyses based on age or respiratory support at entry reported no significant difference in mortality between the arms.<br>• No difference between the arms in the secondary outcome of initiation of ventilation, and no difference in the composite outcome of in-hospital mortality or initiation of ventilation<br>• The number of deaths due to any cardiac cause during the 14 days after enrollment (the dosing period) was lower in these 2 arms than in the other study arms (the RDV, LPV/RTV, and IFN arms and their respective control arms). | |
| **PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21]** | | | |
| Randomized, placebo-controlled, blinded trial in hospitalized adults (n = 479) | **Key Inclusion Criteria:**<br>• Laboratory-confirmed SARS-CoV-2 infection<br>• Symptoms of respiratory illness for <10 days<br>**Key Exclusion Criteria:**<br>• More than 1 dose of HCQ or CQ during the previous 10 days<br>• Prolonged QTc interval (>500 ms)<br>**Interventions:**<br>• HCQ 400 mg PO twice daily for 2 doses, then HCQ 200 mg PO twice daily for 8 doses<br>• Matching placebo<br>**Primary Endpoint:**<br>• Clinical status 14 days after randomization, as measured by a 7-point ordinal scale (the COVID Outcomes Scale) | **Number of Participants:**<br>• Enrollment occurred between April 2 and June 19, 2020.<br>• HCQ (n = 242) and placebo (n = 237)<br>• Planned sample size was 510 participants, but study enrollment was halted early due to futility.<br>**Participant Characteristics:**<br>• Median age was 58 and 57 years in HCQ and placebo arms, respectively; 33% of patients were aged ≥65 years and 24% of patients were Black/African American.<br>• 33% to 36% of patients had diabetes mellitus, 6% to 12% had heart disease, and 7% to 9% had chronic lung disease.<br>• At randomization, 5.4% of patients in HCQ arm and 8% in placebo arm were receiving IMV or ECMO. In both arms, 11% to 12% of patients were receiving noninvasive ventilation or HFNC oxygen, 46% to 48% were receiving low-flow oxygen, and 35% were receiving no respiratory support.<br>• Among the patients who received concomitant medications, 22% received RDV, 19% received AZM, and 18% received corticosteroids. There was no difference in concomitant medication use between the arms. | **Key Limitations:**<br>• It is unclear how the primary outcome of this study (a median COVID Outcomes Scale score) translates to clinical practice.<br>**Interpretation:**<br>• HCQ does not improve patient scores on the COVID Outcomes Scale in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection when compared to placebo.<br>• HCQ did not improve survival or time to discharge in these patients when compared to placebo. |

| Study Design | Methods | Results | Limitations and Interpretation |
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| **PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21]**, continued | | | |
| | | **Outcomes:**<br>• Median COVID Outcomes Scale score was 6 in HCQ arm (IQR 4–7) and 6 in placebo arm (IQR 4–7; aOR 1.02; 95% CI, 0.73–1.42).<br>• No difference between the arms in the secondary outcome of all-cause, all-location death at Day 14 and Day 28<br>• No difference between the arms in the number of any of the following systematically collected safety events: cardiac arrest treated with CPR, symptomatic hypoglycemia, ventricular arrhythmia, or seizure<br>• Among patients who had QTc assessed, 5.9% in HCQ arm and 3.3% in placebo arm had a recorded QTc interval >500 ms during the first 5 days of dosing. | |
| **RECOVERY Trial[22]** | | | |
| Open-label, randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,197) | **Key Inclusion Criteria:**<br>• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection<br>**Key Exclusion Criteria:**<br>• Patients with prolonged QTc intervals were excluded from HCQ arm.<br>**Interventions:**<br>• HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge<br>• Usual SOC<br>**Primary Endpoint:**<br>• All-cause mortality at Day 28 after randomization | **Number of Participants:**<br>• HCQ (n = 1,561) and SOC (n = 3,155)<br>• Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ.<br>**Participant Characteristics:**<br>• Mean age was 65 years in both arms; 41% of patients were aged ≥70 years.<br>• 90% of patients had laboratory-confirmed SARS-CoV-2 infection.<br>• 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease.<br>• At randomization, 17% of patients were receiving IMV or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.<br>• Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone. | **Key Limitations:**<br>• Not blinded<br>• Information on occurrence of new major cardiac arrythmia was not collected throughout the trial.<br>**Interpretation:**<br>• 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.<br>• Patients who received HCQ had a longer median length of hospital stay, and those who were not on IMV 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 |
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| **RECOVERY Trial[22]**, continued | | | |
| | | **Outcomes:**<br>• No significant difference in 28-day mortality between the 2 arms; 421 patients (26.8%) in HCQ arm and 790 patients (27.0%) in SOC arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.97–1.23; *P* = 0.15).<br>• A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,266 participants (90.5%) who had a positive SARS-CoV-2 test result.<br>• Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm.<br>• Patients who received HCQ and who were not on IMV at baseline had an increased risk of requiring intubation and an increased risk of death.<br>• 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 735 patients (47.1%) in HCQ arm and 1,421 patients (45.0%) in SOC arm.<br>• No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention; 1 case of Torsades de Pointes was reported in HCQ arm. | |
| **Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23]** | | | |
| Open-label, 3-arm RCT in hospitalized adults (n = 667) | **Key Inclusion Criteria:**<br>• Aged ≥18 years<br>• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection<br>• Mild or moderate COVID-19<br>• Duration of symptoms ≤14 days | **Number of Participants:**<br>• mITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504).<br>**Participant Characteristics:**<br>• Mean age was 50 years.<br>• 58% of patients were men. | **Key Limitations:**<br>• Not blinded<br>• Follow-up period was restricted to 15 days.<br>**Interpretation:**<br>• Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients |

| Study Design | Methods | Results | Limitations and Interpretation |
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| **Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23]**, continued | | | |
| | **Key Exclusion Criteria:**<br>• Need for >4 L of supplemental oxygen or ≥40% $FiO_2$ by face mask<br>• History of ventricular tachycardia<br>• QT interval ≥480 ms<br>**Interventions:**<br>• HCQ 400 mg twice daily for 7 days plus SOC<br>• HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC<br>• SOC alone<br>**Primary Endpoint:**<br>• Clinical status at Day 15, as measured by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection<br>**Ordinal Scale Definitions:**<br>1. Not hospitalized, no limitations<br>2. Not hospitalized, with limitations<br>3. Hospitalized, not on oxygen<br>4. Hospitalized, on oxygen<br>5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation<br>6. Hospitalized, on mechanical ventilation<br>7. Death | • At baseline, 58.2% of patients were Ordinal Level 3; 41.8% were Ordinal Level 4.<br>• Median time from symptom onset to randomization was 7 days.<br>• 23.3% to 23.9% of patients received oseltamivir.<br>**Outcomes:**<br>• No significant difference in the odds of worse clinical status at Day 15 between 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; $P = 1.00$)<br>• 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"<br>• 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%).<br>• 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. | with mild or moderate COVID-19. |

| Study Design | Methods | Results | Limitations and Interpretation |
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| **Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19[24]** | | | |
| Randomized, placebo-controlled trial in nonhospitalized adults (n = 491) | **Key Inclusion Criteria:**<br>• Symptoms that were compatible with COVID-19 and lasted ≤4 days<br>• Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days<br>**Key Exclusion Criteria:**<br>• Aged <18 years<br>• Hospitalized<br>• Receipt of certain medications<br>**Interventions:**<br>• HCQ 800 mg once, then HCQ 600 mg in 6–8 hours, then HCQ 600 mg once daily for 4 days<br>• Placebo<br>**Primary Endpoints:**<br>• Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death.<br>• Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, measured by a 10-point, self-reported, visual analogue scale | **Number of Participants:**<br>• Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211)<br>**Participant Characteristics:**<br>• 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%).<br>• Median age was 40 years.<br>• 56% of patients were women.<br>• Only 3% of patients were Black.<br>• Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions.<br>• 56% of patients were enrolled on Day 1 of symptom onset.<br>• 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact.<br>**Outcomes:**<br>• 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; $P = 0.117$).<br>• Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$).<br>• No difference in the incidence of hospitalization between the arms (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<br>• A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$). | **Key Limitations:**<br>• This study enrolled a highly heterogeneous population.<br>• Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2.<br>• 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.<br>• This study used surveys for screening, symptom assessment, and adherence reporting.<br>• Visual analogue scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated.<br>**Interpretation:**<br>• 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. |

| Study Design | Methods | Results | Limitations and Interpretation |
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| **Hydroxychloroquine in Nonhospitalized Adults With Mild COVID-19[25]** | | | |
| Open-label RCT in nonhospitalized adults (n = 353) | **Key Inclusion Criteria:**<br>• Laboratory-confirmed SARS-CoV-2 infection<br>• <5 days of mild COVID-19 symptoms<br>**Key Exclusion Criteria:**<br>• Moderate to severe COVID-19<br>• Severe liver or renal disease<br>• History of cardiac arrhythmia<br>• QT prolongation<br>**Interventions:**<br>• HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days<br>• No antiviral treatment (control arm)<br>**Primary Endpoint:**<br>• Reduction in SARS-CoV-2 viral load, assessed using NP swabs on Days 3 and 7<br>**Secondary Endpoints:**<br>• Disease progression up to Day 28<br>• Time to complete resolution of symptoms | **Number of Participants:**<br>• ITT analysis: HCQ (n = 136) and control (n = 157)<br>• 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal.<br>**Participant Characteristics:**<br>• Mean age was 41.6 years.<br>• 67% of patients were woman.<br>• Majority of patients were health care workers (87%).<br>• 53% of patients reported chronic health conditions.<br>• Median time from symptom onset to enrollment was 3 days (IQR 2–4 days).<br>• Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss.<br>**Outcomes:**<br>• No significant difference in viral load reduction between control arm and HCQ arm at Day 3<br>• (-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 log10 copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29).<br>• 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)<br>• 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; $P = 0.38$)<br>• 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."<br>• 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. | **Key Limitations:**<br>• Open-label, non-placebo-controlled trial<br>• Study design allowed for the possibility of dropouts in control arm and over-reporting of AEs in HCQ arm.<br>• The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI.<br>• The majority of the participants were relatively young health care workers.<br>**Interpretation:**<br>• 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 |
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| **Observational Study on Hydroxychloroquine With or Without Azithromycin[26]** | | | |
| Retrospective, multicenter, observational study in a random sample of hospitalized adults with COVID-19 from the New York Department of Health (n = 1,438) | **Key Inclusion Criteria:**<br>• Laboratory-confirmed SARS-CoV-2 infection<br>**Interventions:**<br>• HCQ plus AZM<br>• HCQ alone<br>• AZM alone<br>• Neither drug<br>**Primary Endpoint:**<br>• In-hospital mortality<br>**Secondary Endpoint:**<br>• Cardiac arrest and arrhythmia or QT prolongation on an ECG | **Number of Participants:**<br>• HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221)<br>Participant Characteristics:<br>• Patients in the treatment arms had more severe disease at baseline than those who received neither drug.<br>**Outcomes:**<br>• 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.<br>• 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). | **Key Limitations:**<br>• This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.<br>**Interpretation:**<br>• Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of 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[27]** | | | |
| Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376) | **Key Inclusion Criteria:**<br>• Laboratory-confirmed SARS-CoV-2 infection<br>**Key Exclusion Criteria:**<br>• Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department<br>**Interventions:**<br>• HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days<br>• No HCQ<br>**Primary Endpoint:**<br>• Time from study baseline (24 hours after patients arrived at the ED) to intubation or death | **Number of Participants:**<br>• Received HCQ (n = 811) and did not receive HCQ (n = 565)<br>**Participant Characteristics:**<br>• HCQ recipients were more severely ill at baseline than those who did not receive HCQ.<br>**Outcomes:**<br>• 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).<br>• No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31) | **Key Limitations:**<br>• This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.<br>**Interpretation:**<br>• The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study. |

**Key:** AE = adverse event; AV = atrioventricular; AZM = azithromycin; CPR = cardiopulmonary resuscitation; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = emergency department, $FiO_2$ = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; IFN = interferon; IMV = invasive mechanical ventilation; ITT = intention-to-treat; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care

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