COVID-19: TREATMENT WITH HYDROXYCHLOROQUINE (HCQ)

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated May 18, 2020 3:00 pm  All links rechecked May 17 unless otherwise noted.

This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- Is hydroxychloroquine safe and effective for treatment of COVID-19 disease?
  
  *Use of hydroxychloroquine for prevention of COVID-19 disease is outside the scope of this report.*

Summary of major recommendations

- Use of hydroxychloroquine and chloroquine for treatment of COVID-19 disease is considered an off-label indication. Clinical trials are in progress.
- Current clinical evidence on hydroxychloroquine is from small, low-quality studies, with inconsistent results (GRADE strength of evidence evaluation: very low).
- The most recent guidance discourages use of hydroxychloroquine outside of clinical trials.
- The most recent evidence reviews have stressed the weakness of clinical trials reported to date and the increasing recognition of adverse events from hydroxychloroquine.
- None of the hospitals recommend use of hydroxychloroquine for treatment of outpatients outside of clinical trials.

Guidelines on hydroxychloroquine for treatment of COVID-19 disease

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<th>Source</th>
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<td>NIH</td>
<td>There are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 (strong recommendation, based on expert opinion). The Panel recommends against using high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (strong recommendation, based on RCT evidence) When chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects (AEs), especially prolonged QTc interval (strong recommendation, based on expert opinion). The Panel recommends against the use of hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in the context of a clinical trial (strong recommendation, based on expert opinion).</td>
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<td>Ontario</td>
<td>Chloroquine or hydroxychloroquine is not recommended outside of approved clinical trials or where other indications would justify its use.</td>
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<td>FDA</td>
<td>There are currently no FDA-approved medical countermeasures for COVID-19. Because chloroquine phosphate and hydroxychloroquine may possibly help very sick patients, FDA is allowing these drugs to be provided to certain hospitalized patients under an Emergency Use Authorization issued March 28. Under the EUA, health care providers and patients are provided with information about the risks of these drugs. However, more data from clinical trials are necessary for us to determine whether chloroquine phosphate or hydroxychloroquine sulfate are safe and effective in treating or preventing COVID-19. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.</td>
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If a healthcare professional is considering use of hydroxychloroquine or chloroquine to treat or prevent COVID-19, FDA recommends checking www.clinicaltrials.gov for a suitable clinical trial and consider enrolling the patient. Consider using resources available to assess a patient’s risk of QT prolongation and mortality. Emergency Use Authorization is only applicable to hospitalized patients.

The uncertain nature of the data documenting the efficacy of these drugs does not support recommending the use of chloroquine or hydroxychloroquine, with or without azithromycin, outside of a research protocol in patients with a confirmed diagnosis of COVID-19 whose clinical condition requires hospitalization. (scientific evidence level: insufficient)

No data support recommending the use of chloroquine or hydroxychloroquine outside of a research protocol in patients with a confirmed diagnosis of COVID-19 whose clinical condition does not require hospitalization. (scientific evidence level: insufficient)

There are no drugs or other therapeutics presently approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated.

ACP advises against use of chloroquine or hydroxychloroquine alone or in combination with azithromycin as treatment for COVID-19, and recommends shared and informed decision making if hospitalized patients are treated with either drug alone or in combination with azithromycin in the context of a clinical trial.

Evidence reviews on hydroxychloroquine for treatment of COVID-19 disease

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<td>ACP</td>
<td>Safety is of concern, because QTc prolongation with torsadogenic potential is a known risk. Use in patients with a critical illness such as COVID-19, which is often accompanied by electrolyte abnormalities, raises additional concern. In a phase Ib clinical trial to assess safety and efficacy of two dose regimens of chloroquine (600mg twice daily for 10 days, or 450mg twice daily on 1 day then once daily for 4 days) combined with both ceftriaxone and azithromycin, 25% of the patients in the higher dose treatment arm presented with QTc&gt;500ms. The study was halted prematurely due to safety concerns. Chloroquine dosages used in various trials are otherwise summarized in a recent narrative review. FDA posted a statement &quot;Reiterates Importance of Close Patient Supervision for ‘Off-Label’ Use of Antimalarial Drugs to Mitigate Known Risks, Including Heart Rhythm Problems.&quot; More safety data and data from high-quality clinical trials are urgently needed. Effectiveness is likely limited. Early in vitro data suggested effectiveness in reducing viral infection and small nonrandomized early observational reports suggested benefit, but higher quality and larger data sets have been without significant evidence of clinical benefit. In the above phase Ib safety and efficacy trial for two dose regimens of chloroquine, at the time of discontinuation the fatality rate for the higher dose chloroquine arm was 13.5% (95%CI=6.9-23.0%), overlapping historic patient data, and in 14 patients with paired samples, respiratory secretion at day 4 was negative in only one patient. A prospective controlled clinical trial of hydroxychloroquine with 30 enrolled patients demonstrated no clinical benefit over usual supportive care. A randomized parallel-group trial of 62 patients (non-peer-reviewed) showed shorter time to clinical recovery (without a measured mortality endpoint). In France, 84 patients requiring oxygen who received hydroxychloroquine 600 mg daily did not differ from 97 similar but nonrandomized control patients in their rates of transfer to the ICU or all-cause death at 7 days. A non-peer-reviewed, preprint, retrospective analysis of 368 non-randomized, hospitalized patients with confirmed SARS-CoV-2 infection from all United States Veterans Health Administration medical centers found that use of hydroxychloroquine alone or with azithromycin was not associated with reduction of either mechanical ventilation or mortality; an association with increased overall mortality was identified retrospectively in nonrandomized patients treated with hydroxychloroquine alone. An observational study of 1376 consecutive, non-randomized patients hospitalized at least 24 hours with COVID-19 excluded those who were intubated during their first 24 hours. Those who received hydroxychloroquine did not</td>
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A new database search found 158 trials investigating chloroquine and hydroxychloroquine as active treatments. Current data do not support the use of hydroxychloroquine for prophylaxis or treatment of COVID-19.

Growing safety signals that high dose or use in severely ill patients may contribute to cardiotoxicity. Chloroquine is not generally available in the U.S.; many reporting shortages of hydroxychloroquine.

**Supportive Evidence for Hydroxychloroquine**: Small randomized trials—with inherent weaknesses—seem to show modest benefit from Hydroxychloroquine. In one study, investigators showed significant improvement in time to clinical recovery, symptoms and pneumonia (by CT scan) when compared to the control arm. In another study, investigators found those with mild-moderate disease had modest alleviation of symptoms but no difference in seroconversion. A systematic review/meta-analysis of seven studies revealed that Hydroxychloroquine may improve symptoms and decrease radiological progression of lung disease but no difference in death or clinical worsening of disease. Notably the authors note no difference in safety. The authors advocated for more studies.

**Evidence Against Hydroxychloroquine/Chloroquine**: One study failed to demonstrate a benefit among patients hospitalized with an oxygen requirement. A retrospective VA analysis concluded no reduction in risk of mechanical ventilation and in fact found an association of increased overall mortality with use of Hydroxychloroquine. Further adding to the potential harm of these medications, one study showed cardiac adverse events when using a higher dosage of chloroquine. In a large, observational study, investigators in New York found no significant association with the medication and intubation or death.

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<td>Southern Cal.</td>
<td>Early in the pandemic, Hydroxychloroquine was suggested as a potential antiviral medication based on the medications’ cellular interaction with the virus and in vitro data. Initial anecdotal evidence suggested the medication helps with pneumonia in regards to shortening of disease course and improvement of lung imaging. This led to the CDC suggesting the use of Hydroxychloroquine and the FDA enacting its emergency use without rigorous clinical trials. This has led to much controversy given potential for cardiac complications, prompting medical experts to advocate for caution. The FDA issued a safety communication cautioning “against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.”</td>
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| Hopkins         | The overall feeling is that safety is an issue especially in more severely ill patients; however, it remains without high-quality data to argue for or against its use. Reported to have some efficacy in vitro and in limited, very low-quality evidence for COVID-19 pneumonia. The mechanism may be by interfering with cellular acidification in the phagolysosome.  
- Much hype and preliminary reports of efficacy are from press releases or small studies.  
- Gautret et al. suggest decreased SARS-CoV-2 shedding in non-RCT of 36 patients; 6 patients in a post-hoc analysis who received HCQ combined with azithromycin had further viral carriage reduction.  
- Original journal accepting this paper has withdrawn it from consideration due to the paper not being of the characteristics and standards for the journal.  
- Small sample size, lack of clinical outcomes, exclusion of patients who died or went to ICU, lack of paired stepwise statistical comparison means clinicians ought to not base decisions on these limited results, despite the widely interpreted lay conclusion that that HCQ + AZ is an effective combination.  
- Chen et al in an unpublished RCT of 30 patients did not find HCQ provided benefit.  
- The study suggests that if HCQ has an impact, it is likely small.  
- Chloroquine is not generally available in the U.S.; many reporting shortages of hydroxychloroquine.  
- Growing safety signals that high dose or use in severely ill patients may contribute to cardiotoxicity. HCQ may cause prolonged QT, and caution should be used in critically ill COVID-19 patients who may have cardiac dysfunction or if combined with other drugs that cause QT prolongation. |
| CEBM            | Current data do not support the use of hydroxychloroquine for prophylaxis or treatment of COVID-19. There are no published trials of prophylaxis. Two trials of hydroxychloroquine treatment that are in the public domain, one non-peer reviewed, are premature analyses of trials whose conduct in both cases diverged from the published skeleton protocols registered on clinical trial sites. Neither they, nor three other negative trials that have since appeared, support the view that hydroxychloroquine is effective in the management of even mild COVID-19 disease.  
- A new database search found 158 trials investigating chloroquine and hydroxychloroquine as active treatments, with planned enrollment of over 137,000 patients (includes prophylactic studies) Just 52 trials (33%) meet the highest design standard. The number of new trials registered has dropped from 57 in the week of April 9 to 10 the week of April 26. |
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<td>NIH May 12</td>
<td>Chloroquine and hydroxychloroquine have been used in small randomized trials and in some case series and clinical trials with conflicting study reports (as described below). Both drugs are available through the Strategic National Stockpile for hospitalized adults and adolescents weighing ≥50 kg who cannot access these drugs through a clinical trial. Reports have documented serious dysrhythmias in patients with COVID-19 treated with chloroquine or hydroxychloroquine, often in combination with azithromycin and other medicines that prolong the QTc interval. Given the risk of dysrhythmias, the Food and Drug Administration (FDA) cautions against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of the setting of a hospital or clinical trial. 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 comparative trial compared high-dose chloroquine versus low-dose chloroquine in patients with COVID-19; in addition, all of the 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. Study results and limitations are described in detail in the guideline document.</td>
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<td>ASHP May 8</td>
<td>Only limited clinical trial data available to date to evaluate use of hydroxychloroquine for treatment or prevention of COVID-19. Clinical experience in treating pts with COVID-19 accumulating; only limited data available to date to support efficacy and identify possible safety concerns in pts with COVID-19. Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 is not established. Additional data needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy for treatment or prevention of COVID19. Additional data needed to substantiate initial reports of efficacy for treatment and identify optimal dose and duration. Additional data needed before any conclusions can be made regarding possible benefits and safety of using hydroxychloroquine with azithromycin. Data needed regarding toxicity profile when used in patients with COVID-19 See Appendix for results of studies reported in ASHP evidence table.</td>
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### Medical center guidance on hydroxychloroquine for treatment of COVID-19

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<td>Penn Medicine May 15</td>
<td>Hydroxychloroquine should not be used for routine clinical care of patients with SARS-CoV-2. Supportive care is preferred until additional data evaluating the efficacy of this and other medications are available. Due to emerging data raising concerns about safety and efficacy of hydroxychloroquine and chloroquine and recommendations from professional societies and public health agencies, hydroxychloroquine should be considered only in the setting of clinical trials. Hospitalized patients (including critically ill): There are no data to support routine use of hydroxychloroquine to treat these patients, and there are safety concerns from available data on chloroquine and hydroxychloroquine so use is recommended only in setting of clinical trial. Non-hospitalized patients: Based on available data on chloroquine and hydroxychloroquine risk of hydroxychloroquine outweighs any theoretical benefit for non-hospitalized patients outside of a clinical trial. There are significant safety concerns in patients that cannot be closely monitored.</td>
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Hospital | Policy/recommendation
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**Brigham**<br>May 12 | **Mild disease**: Not recommended at this time given lack of data and limited supplies of investigational agents.<br>**Moderate disease** (SpO\textsubscript{2} > 94% on room air): Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine or favipiravir via an RCT.<br>**Severe disease**: Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine or favipiravir via an RCT. Can consider remdesivir via emergency use authorization if certain in-house criteria are met and supply is available. Consider tocilizumab, canakinumab, or sarilumab via RCTs.<br>**Severe disease with critical illness** (respiratory failure, systemic inflammatory response syndrome, multi-organ failure): Consider remdesivir via open label clinical trial. If not eligible, consider hydroxychloroquine via an RCT. Can consider remdesivir via emergency use authorization if certain in-house criteria are met and supply is available. Consider sarilumab via RCTs. If not eligible, consider risks and benefits of use of off-label anti-inflammatory therapies (tocilizumab, anakinra, steroids)<br>**Pregnant patients**: In severe disease, consider remdesivir via compassionate use. If remdesivir cannot be used, weigh risks and benefits of hydroxychloroquine.

**Mass., General**<br>May 8 | For hospitalized patients with severe or critical disease**: We generally favor not initiating HCQ outside of clinical trial, but it may be considered on a case by case basis. Note chloroquine has activity but limited supply and safety concerns so hydroxychloroquine preferred.<br>For hospitalized patients whose disease is mild or moderate: Supportive care recommended, hydroxychloroquine or chloroquine not indicated in these patients.

**Washington**<br>May 7 | Inpatients with lower respiratory tract infection and oxygen requirement or mechanical ventilation: Hydroxychloroquine is no longer recommended. Recommend clinical trial. If HCQ is started outside of a clinical trial, obtain baseline EKG and share decision-making with the patient. Note: Starting HCQ may disqualify from clinical trial enrollment.<br>Outpatients: Hydroxychloroquine is not recommended. Consider clinical trial enrollment.<br>Recent clinical studies have not demonstrated virologic or clinical benefits, see evidence summary for details.

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**Key to sources referenced**

ACP—American College of Physicians<br>ASHP—American Society of Health System Pharmacists<br>CEBM—University of Oxford Centre for Evidence-based Medicine<br>CPA—Canadian Pharmacists Association<br>IDSA—Infectious Disease Society of America<br>INESSS—Institut national d'excellence en santé et services sociaux (Québec)<br>NIH—National Institutes of Health COVID-19 Treatment Guidelines Panel<br>Ontario—University Health Network Antimicrobial Stewardship Program<br>SIDP—Society of Infectious Disease Pharmacists

**Update history (key additions and changes)**

May 18: Updated NIH and hospital guidance and evidence reviews, new evidence review from ACP. Guidance more than one month old has been removed from the tables. Hospital evidence reviews incorporated into evidence review table. No changes to summary conclusions.

April 30: New guidance from NIH, updated guidance from FDA and CPA. New evidence reviews from MGH (FLARE), NIH and CADTH, updated reviews from CEBM and SIDP. Guidance more than one month old has been removed from the tables. Updated hospital guidance. New conclusions regarding guidance discouraging use outside clinical trials because of uncertain benefits and risk of adverse events.

April 22: More detailed hospital guidance: some hospitals now testing HCQ in outpatient clinical trials, evidence review table streamlined.
April 14: Initial report

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site for further details on the methods for developing these reports.

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Evidence team leader: Emilia J. Flores, PhD, RN (CEP)
Reviewer: Nikhil K. Mull, MD (CEP)

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Appendix. Studies in ASHP evidence table as of May 17, 2020

Hydroxychloroquine small pilot study conducted in China: 15 treatment-naive pts received hydroxychloroquine sulfate (400 mg daily for 5 days) with conventional treatments and 15 pts received conventional treatments alone; both groups received interferon and most pts also received umifenovir (Arbidol®) or LPV/RTV. Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 pts (86.7%) treated with hydroxychloroquine and 14 pts (93.3%) not treated with the drug (data unclear for 3 pts); median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups; evidence of radiologic progression on CT in 5 pts treated with the drug and 7 pts not treated with the drug (all pts showed improvement at follow-up).

Hydroxychloroquine randomized, parallel group study in adults in China (ChiCTR2000029559): 31 pts with COVID19 and pneumonia received hydroxychloroquine sulfate (200 mg twice daily for 5 days) and standard treatment (O2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids) and 31 other pts received standard treatment alone (control group). Exclusion criteria included severe and critical illness. Pts assessed at baseline and 5 days after treatment initiation for time to clinical recovery (TTCR; defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that hydroxychloroquine was associated with symptom relief since time to fever normalization was shorter in hydroxychloroquine group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in hydroxychloroquine group, and pneumonia improved in 25/31 pts (80.6%) in hydroxychloroquine group vs 17/31 pts (54.8%) in control group. Total of 4 pts progressed to severe illness (all in the control group).

31 Note: This study did not include pts with severe disease and pts received other anti-infectives in addition to hydroxychloroquine. At study entry, 9 pts without fever and 9 pts without cough were included in hydroxychloroquine group and 14 pts without fever and 16 pts without cough were included in control group; unclear how these pts were addressed in TTCR calculations. Although initial registered study protocol specified 2 different hydroxychloroquine treatment groups and a placebo group (each with 100 pts) and primary end points of time to negative nucleic acid and T-cell recovery, data provided only for certain clinical symptoms in 62 pts without severe disease and PCR results not reported.

Hydroxychloroquine with azithromycin open-label, nonrandomized study in France: Preliminary data from an ongoing study in hospitalized pts with confirmed COVID-19 was used to assess efficacy of hydroxychloroquine used alone or with azithromycin; untreated pts were used as a negative control. The primary end point was negative PCR results in nasopharyngeal samples at day 6. Data from 14 pts treated with hydroxychloroquine (200 mg 3 times daily for 10 days), 6 pts treated with hydroxychloroquine and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5), and 16 pts in the control group were analyzed. At day 6, 8/14 (57%) in the hydroxychloroquine group, 6/6 (100%) in the hydroxychloroquine and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results. At day 8, a positive PCR was reported in a pt treated with both drugs who had tested negative at day 6. Note: This was a small nonrandomized study that didn't appear to be designed to compare hydroxychloroquine vs hydroxychloroquine and azithromycin (pts received antibiotics to prevent bacterial superinfection based on clinical judgment). Data on disease severity was unclear (some asymptomatic pts were included when study initiated) and information on disease progression and clinical outcomes was not presented.
**Hydroxychloroquine with azithromycin open-label, uncontrolled study in France:** 11 adults hospitalized with COVID-19 received hydroxychloroquine (600 mg daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). At time of treatment initiation, 8/11 pts had significant comorbidities associated with poor outcomes and 10/11 had fever and received O2. Within 5 days, 1 pt died and 2 transferred to ICU; the regimen discontinued in 1 pt after 4 days because of prolonged QT interval. Nasopharyngeal samples were still PCR positive at days 5 and 6 in 8/10 pts tested. Note: In this small uncontrolled study, hydroxychloroquine and azithromycin regimen did not result in rapid viral clearance or provide clinical benefit.

**Hydroxychloroquine with azithromycin uncontrolled, observational study in France:** 80 adults with confirmed COVID19 were treated with hydroxychloroquine (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration (low national early warning score for COVID-19 based on age, respiratory rate, O₂ saturation, temperature, BP, pulse, level of consciousness); only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in infectious disease (ID) unit were evaluated in pts who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O₂; 3 pts transferred to ICU; 1 pt died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested. Note: Almost all pts were considered low risk for clinical deterioration (including 4 pts described as asymptomatic carriers) and it is unclear how many would have had spontaneous conversion to negative nasopharyngeal samples during same time frame. Although 80 pts were enrolled, PCR results available for fewer pts beginning on day 3 and only 60 pts represented in day 6 data. This was an uncontrolled study and data presented cannot be used to determine whether a regimen of hydroxychloroquine with azithromycin provides benefits in terms of disease progression or decreased infectiousness, especially for pts with more severe disease.

**Hydroxychloroquine (with or without azithromycin) in a retrospective analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers:** Data for 368 males (median age >65 years) treated with hydroxychloroquine in addition to standard supportive management were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in those treated with hydroxychloroquine, 22.1% (25/113) in those treated with hydroxychloroquine and azithromycin, and 11.4% (18/158) in those not treated with hydroxychloroquine; rate of ventilation was 13.3, 6.9, and 14.1%, respectively. Use of hydroxychloroquine alone (but not use of hydroxychloroquine and azithromycin) was associated with increased overall mortality compared with no hydroxychloroquine; use of hydroxychloroquine with or without azithromycin did not reduce the risk of mechanical ventilation. Note: The patient population included only elderly males 59-75 years of age, many with significant comorbidities. This analysis did not look at efficacy measures.

**Efficacy measures:** Initial studies evaluating hydroxychloroquine based efficacy of the drug on negative conversion in nasopharyngeal samples at day 6 or 7. RTPCR tests using upper and lower respiratory specimens (including nasopharyngeal and oropharyngeal swabs) are recommended for diagnosis of COVID-19; however, dynamics of SARS-Cov-2 in infected patients (untreated or treated) and presence of the virus at various body sites over the course of infection have not been fully determined.