Rapid Evidence Review

Clinical evidence for the use of antivirals in the treatment of COVID-19

Version 10, 26th June 2020

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

Prepared by the COVID-19 Evidence Review Group

This Rapid Evidence Review is updated on a regular basis with the most recent version available *here*.

Key changes (highlighted in yellow) between version 9 (12th June 2020) and version 10 (26th June 2020): Press-releases announcing the stopping of recruitment the hydroxychloroquine arms of the SOLIDARITY clinical trial and the ORCHID clinical trial; Press-release announcing MHRA request to UK clinical trialists to suspend recruitment into hydroxychloroquine arms of COVID-19 studies; retraction of preprint from Kim et al reporting comparative efficacy of hydroxychloroquine, lopinavir-ritonavir and conservative treatment; remdesivir recommended for EMA authorisation; Sbidian et al trial of hydroxychloroquine with/without azithromycin versus Neither drug; Updated IDSA guidelines.

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Emerging randomised control trials (RCTs) and observational cohort studies on the efficacy of antiviral treatments for COVID-19 have provided inconsistent results. Many of these studies have been of very low quality; limited by small sample sizes, unclear methods, lack of a control arm or lack of blinding or randomisation where control arms are present, unadjusted analyses, and sub-optimal reporting. High-quality, methodologically robust clinical trials, in large numbers of patients are ongoing, and essential to provide credible evidence on the efficacy and safety of investigational antiviral agents for COVID-19.

Please note that some of the articles included in this review are 'pre-prints' i.e. unpublished, non-peer-reviewed scientific manuscripts[1].

Summary of evidence on the clinical efficacy of hydroxychloroquine

Emerging evidence is increasingly showing a lack of benefit of hydroxychloroquine for the treatment of COVID-19. This follows on from earlier studies which reported inconsistent findings. The evidence for hydroxychloroquine efficacy is limited to press-releases announcing interim results from two large, open-label RCTs, two small RCTs and a growing number of observational, mostly retrospective, cohort studies. Three of the largest international trials of antivirals for COVID-19, the WHO SOLIDARITY, the UK RECOVERY trial and the US ORCHID trial, have stopped enrolling patients to the hydroxychloroquine arm of the study, following interim results which showed no clinical benefit. Following consideration of trial results, the UK's medicines regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), instructed UK clinical trialists using hydroxychloroquine for COVID-19 to suspend recruitment of further participants (1).

Randomised controlled trials

Preliminary results from the **RECOVERY trial (05/06/20)**, a randomised, open-label trial investigating the efficacy of a number of treatments for patients hospitalised with COVID-19, reported no significant difference in 28-day mortality among 1542 patients treated with hydroxychloroquine and 3132 patients treated with usual care (25.7% hydroxychloroquine vs. 23.5% usual care; HR 1.11 95% CI 0.98-1.26; p=0.10). There was

[1]*Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints". These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.*

also no evidence of beneficial effects on hospital stay duration or other outcomes. Full results of the study have yet to be published (2).

A press release from the **WHO SOLIDARITY trial (17/06/20)** announced that data showed that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care.

Two small RCTs, one open-label and one double-blind, have assessed the efficacy and safety of hydroxychloroquine plus standard of care (SoC) versus SoC alone in hospitalised patients in China, with predominantly mild/moderate disease(3, 4). One of the studies, an open-label study conducted in 150 patients **(Tang, 07/05/20)**, found no difference between treatment groups in SARS-CoV-2 negative conversion rate on RT-PCR, or time to negative conversion up to 28 days (4). The dose of hydroxychloroquine (1200mg daily for three days, followed by 800mg daily for 2-3 weeks) was higher than has been reported for other studies. The other double-blind RCT, conducted in 62 patients **(Chen, 30/03/20)**, reported a modest reduction (approximately one day) in time to fever and cough recovery in patients treated with hydroxychloroquine 400 mg daily for five days, compared with SoC alone (3). Improvement in pneumonia, assessed by chest CT, occurred in a greater proportion of patients in the hydroxychloroquine group compared with the control group (80.6% vs 54.8%) (3).

An abstract of a Chinese RCT (n=30) suggested no difference in viral clearance between hydroxychloroquine-treated patients and a control group **(Chen, 06/03/20)** (5).

The quality and reliability of studies on the efficacy of hydroxychloroquine were initially limited by open-label, non-randomised, uncontrolled study designs, small patient numbers and short follow-up. Larger RCTs are now emerging, though limitations are still notable including the potential for confounding from concomitant antiviral therapies, and inconsistency between the doses of hydroxychloroquine used.

Observational cohort studies

A growing number of retrospective, observational cohort studies now comprise the bulk of the evidence for hydroxychloroquine. These studies have retrospectively analysed data on hospitalised patients to investigate associations between hydroxychloroquine treatment (with/without azithromycin) and clinical/virological outcomes in patients with COVID-19. The analysis and interpretation of data from these non-randomised, retrospective studies is critically dependent on the use of appropriate statistical methods of adjustment which minimise the potential for bias and confounding. Even with such adjustment however, there is still a potential for residual confounding to remain, particularly in smaller studies where it is difficult to reliably adjust for multiple confounders. While many of these studies have been peer-reviewed and published in scientific journals, the reliability of this process has been questioned following the controversial publication of an influential study by Mehra et.al on 22/05/20 (6). The study findings led to the temporary suspension of international trials, pending DSMC review of

interim data. Trials were subsequently restarted following the safety reviews. External reviewers questioned the provenance and validity of the data in the Mehra study (7). On 04th June 2020, three of the study authors requested that the paper be redacted as they can no longer vouch for the veracity of the primary data sources (8).

A retrospective cohort study in a non-selected, exhaustive population of 4,642 hospitalised patients with COVID-19 across 39 hospitals in France, found no evidence for efficacy of hydroxychloroquine or hydroxychloroquine+azithromycin on 28-day mortality **(Sibian, 19/06/20) (9).** Significant differences in baseline characteristics were observed. Confounding due to interaction between treatment assignment and baseline covariates, was accounted for using augmented inverse probability of treatment weighting (AIPTW) estimators of average treatment effects. A non-significant trend towards higher mortality with hydroxychloroquine+azithromycin was identified. Significantly higher rates of 28-day discharge home were observed in patients treated with hydroxychloroquine alone. The baseline disease severity of the cohort is unclear due to the lack of respiratory parameters such as oxygenation, ventilation etc.

A retrospective study, using electronic health records of 2,512 patients hospitalised with COVID-19, found that hydroxychloroquine, either alone or with azithromycin, was not associated with increased survival **(Ip, 25/05/20) (10)**. The 30-day mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, respectively. The median time from symptom-onset to hospitalisation was 5 days. Though propensity score modelling was used to mitigate observed imbalances across treatment groups, the extent of these imbalances is not clear as baseline characteristics according to treatment group were not provided.

A peer-reviewed, observational study in a New York hospital retrospectively analysed data on 1376 consecutive patients hospitalised with COVID-19 (excluding those who were intubated, died or discharged within 24 hours of study baseline) **(Geleris, 07/05/20)** (11). The association between hydroxychloroquine use and the primary endpoint – time from study baseline to intubation or death – was estimated by multivariable Cox regression models, inverse-probability-weighted using propensity score methods. Hydroxychloroquine was received by 811 patients, 85.9% of whom were treated within 48 hours, and 565 patients did not receive hydroxychloroquine. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine. Azithromycin was received by 59.9% and 22.5% of patients in the hydroxychloroquine group and no-hydroxychloroquine group respectively. The median follow-up was 22.5 days. In primary analysis, adjusting for observed confounders, there was no significant association between hydroxychloroquine use and intubation or death (HR 1.04; 95% CI, 0.82 to 1.32). There was also no significant association between

treatment with azithromycin and the composite end point (HR 1.03; 95% CI, 0.81 to 1.31) (11).

A peer-reviewed, observational study across 25 hospitals in New York State retrospectively analysed data from a random sample of 1438 hospitalised patients with COVID-19 **(Rosenberg, 11/05/20) (12)**. The primary outcome was in-hospital mortality, with additional secondary outcomes of cardiac arrest and abnormal electrocardiographic findings. A Cox proportional hazards model, fit for time to death, controlling for treatment group and potential confounders, was used to examine the association between hydroxychloroquine use and intubation or death. Of the patients included in the analysis, 735 (51.1%) received hydroxychloroquine+azithromycin, 271 (18.8%) received hydroxychloroquine alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither drug. There were differences between unadjusted groups in baseline demographics, co-morbidities and disease severity. Patients in treatment groups had more clinically severe disease than the neither drug group. Patients receiving hydroxychloroquine, alone or in combination, had higher levels of ICU admission and mechanical ventilation. Following adjustment for potential confounders, no significant differences in mortality were found between patients receiving hydroxychloroquine+azithromycin (adjusted HR, 1.35, 95% CI 0.76 to 2.40), hydroxychloroquine alone (adjusted HR, 1.08, 95% CI 0.63 to 1.85), or azithromycin alone (adjusted HR, 0 .56, 95% CI 0.26 to 1.21), compared with neither drug. Cardiac arrest was more likely in patients receiving hydroxychloroquine+azithromycin compared with those receiving neither drug (adjusted OR, 2.13 95% CI, 1.12 to 4.05; E-value = 1.31).

A peer-reviewed, retrospective analysis of data from 368 patients treated in United States Veterans Health Administration medical centres **(Magagnoli, 21/04/20)**, concluded that hydroxychloroquine use with or without co-administration of azithromycin did not improve mortality or reduce the need for mechanical ventilation in hospitalised patients (13). In fact, hydroxychloroquine use alone was associated with an increased risk of mortality compared to standard care alone. More severe disease was observed in patients on active treatment and while confounding due to selection bias was controlled for by the use of propensity score methodology, there was a lack of detail on the exact methods used(13).

A retrospective analysis of 568 critically ill patients with COVID-19 **(Yu, 01/05/20)**, 48 of whom received hydroxychloroquine (oral 200mg twice daily for 7-10 days) found that hydroxychloroquine treatment is significantly associated with a decreased mortality (45.8% (235/520) in the no-hydroxychloroquine group and 18.8% (9/48) in the hydroxychloroquine group (adjusted HR 0.32, 95% CI 0.16 to 0.62: $p<0.001$)) (14). This effect was suggested to be due to attenuation of inflammatory cytokine storm, due to the observation of a significant reduction in IL-6 levels from baseline in patients treated with hydroxychloroquine, and a return to levels of the control group after treatment

discontinuation. Key details of disease severity and laboratory results for this critically ill cohort are missing, and therefore it is unclear whether the analytical methods used were appropriate to account for the potential bias associated with non-random treatment allocation (14).

Two non-randomised French studies reported conflicting results of analyses comparing hydroxychloroquine 600mg daily with a control (no hydroxychloroquine) group(15, 16). In the larger of the two studies **(Mahevas, 14/04/20)** all patients with SARS-CoV-2 pneumonia admitted to four French hospitals and requiring oxygen support, were included in the retrospective analysis. Outcomes of 84 patients who received hydroxychloroquine within 48 hours of admission were compared with patients who received SoC without hydroxychloroquine. The study used an inverse probability of treatment weighting (IPTW) approach to "emulate" randomisation and balance the differences in baseline variables between treatment groups, using a propensity score model (16). Hydroxychloroquine treatment was not associated with an improvement in survival without transfer to the intensive care unit, or without ARDS, at day 21. In contrast, the other French non-randomised, controlled study **(Gautret, 20/03/20)**, including 42 patients treated with hydroxychloroquine or a control group, reported a higher rate of virological cure in the hydroxychloroquine-treated group at day six post-inclusion (15). A number of additional limitations pertain to this study, including biased methods of assignment of patients to treatment groups, the omission of intention-to-treat analysis. Although patients were prospectively enrolled to the treatment arm in this study, the control group is not considered to provide a robust comparison, due to the method of recruitment i.e. patients who refused treatment and patients recruited from other treatment centres. An intention-to-treat analysis was not conducted.

A retrospective analysis of data from patients who received hydroxychloroquine and azithromycin plus zinc (n=411) versus hydroxychloroquine and azithromycin alone (n=521) **(Carlucci, 08/05/20) (17)**, found that the addition of zinc sulfate to hydroxychloroquine and azithromycin was associated with a decrease in mortality or transition to hospice among patients who did not require ICU level of care. The findings of this study have limited clinical relevance in the absence of a control arm comprising patients who did not receive hydroxychloroquine as the efficacy of this treatment, alone or in combination, has not been proven.

In a small, retrospective observational study (N=34) **(Mallat, 02/05/20)**, multiple linear regression analysis found that hydroxychloroquine was associated with a slower viral clearance in COVID-19 patients with mild to moderate disease, compared with patients who receiving SoC (18). Although results were adjusted for confounding, this was limited to symptoms, pneumonia or oxygen therapy and didn't address the imbalances between treatment groups in baseline characteristics.

Three case-series on the use of combination therapy with hydroxychloroquine and azithromycin report conflicting results, though there may be differences in the study populations (19-21). All studies have reported higher incidences of adverse events in patients treated with hydroxychloroquine, including changes on electrocardiogram (ECG).

Summary of consensus guidelines on hydroxychloroquine for COVID-19

Infectious Diseases Society of America (updated 18/06/2020) (22)	• Recommended for hospitalised patients with COVID-19 **only** in the context of a clinical trial, because of uncertainty regarding its risks and benefits. (Knowledge gap) • Suggests against hydroxychloroquine in combination with azithromycin outside of the context of a clinical trial, because of the potential for toxicity. (Conditional recommendation, very low certainty of evidence)
American Thoracic Society (updated 03/04/2020) (23)	• No suggestion for or against hydroxychloroquine/chloroquine for outpatients, or hospitalised patients with no evidence of pneumonia: • Suggested for hospitalised patients with evidence of pneumonia, if: - Shared decision making with the patient is utilised, and - Suitable data is collected for research, and - Clinical condition is severe enough to warrant treatment, and - There is not a shortage of drug supply
Surviving Sepsis Campaign (updated 28/03/2020) (24)	Insufficient evidence to issue a recommendation in critically ill adults with COVID-19
National Institutes of Health (NIH, updated 12/05/20) (25)	• Recommends against the use of chloroquine or hydroxychloroquine except in a clinical trial setting. (Strong recommendation on the basis of one or more well-designed, non-randomised trials or observational studies)
American College of Physicians (ACP, updated 13/04/20) (26)	• Do not use chloroquine or hydroxychloroquine treatment alone or in combination with azithromycin due to known harms and no available evidence of benefits • Clinicians may treat hospitalised patients with chloroquine or hydroxychloroquine alone or in combination with azithromycin in

	the context of a clinical trial, using shared and informed decision making with patients (and their families)

Summary of evidence on the clinical efficacy of lopinavir-ritonavir

The clinical evidence for comparative efficacy is limited to three open-label/single-blind RCTs (two of which failed to demonstrate a benefit for lopinavir–ritonavir versus SoC, and one which did not include a SoC control arm) and observational case reports (27-31) . The open-label/single-blind design of the RCTs is a limitation as this may lead to performance-bias and detection-bias for subjective outcomes.

In one RCT **(Cao, 18/03/20)** in 199 patients with severe COVID-19, no difference in the time to clinical improvement (based on a seven-category ordinal scale) was observed between lopinavir-ritonavir and SoC (HR for clinical improvement, 1.24; 95% CI, 0.90 to 1.72). Numerical differences in favour of lopinavir-ritonavir were observed in a number of secondary outcomes, including a shorter stay in the intensive care unit (6 days vs. 11 days; difference, -5 days; 95% CI, -9 to 0), but these were not significant. Post-hoc analysis showed that earlier initiation (within 12 days of symptom-onset) was associated with a greater numerical difference in mortality compared to later initiation.

A small RCT in a mild/moderate COVID-19 cohort **(Li, 15/04/20)**, randomised 86 patients 2:2:1 to lopinavir-ritonavir, Arbidol® (umifenovir) or no antiviral treatment for 7-14 days (30). The study was blind to participants and data reviewers but open-label to recruiting physicians. The time from onset to treatment ranged from 3.5 to 6 days across the treatment groups. The mean time to positive-to-negative conversion of SARS-CoV-2 nucleic acid during the 21-day follow-up period was not significantly different between the treatment groups. More patients treated with lopinavir-ritonavir progressed from mild/moderate to severe/critical status than the other two groups.

An open-label RCT in 127 patients with mild COVID-19 **(Hung, 08/05/20)**, randomised patients to combination therapy with lopinavir-ritonavir/ribavirin/interferon beta-1b or lopinavir-ritonavir alone. Interferon was included in the combination therapy arm only in patients recruited up to day 7 of symptom onset. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal RT-PCR SARS-CoV-2 swab than the control group (7 days vs 12 days, HR 4.37, 95% CI 1.86 to 10.24: p=0.0010). This finding was driven by the subgroup of patients (approximately 60%) who were treated within 7 days of symptom-onset with triple-combination therapy, as no significant differences in outcomes were observed in the subgroup of patients treated 7 days or more after symptoms onset (with lopinavir-ritonavir and ribavirin only). The absence of a control arm comprising patients who were treated with SoC is a limitation of this study as the efficacy of lopinavir-ritonavir, alone or in combination, has not been proven. It is difficult to discern between the benefits of early combination treatment and the inclusion of interferon-beta in the combination regimen,

as interferon-beta was omitted from the regimen in patients recruited after day 7 of symptom-onset.

Summary of consensus guidelines on lopinavir-ritonavir

Infectious Diseases Society of America (updated 22/06/2020) (22)	Recommended for hospitalised patients with COVID-19 **only** in the context of a clinical trial, based on failure to show a measurable antiviral effect in an RCT. (Knowledge gap)
American Thoracic Society (updated 03/04/2020) (23)	No suggestion for or against lopinavir-ritonavir for hospitalised patients who have evidence of pneumonia, due to lack of definitive evidence regarding benefit and frequent gastrointestinal side effects
Surviving Sepsis Campaign (updated 28/03/2020) (24)	Suggest against the routine use of lopinavir/ritonavir in critically ill adults with COVID-19 (weak recommendation, low-quality evidence)
National Institutes of Health (NIH, updated 12/05/20) (25)	Recommends against use of lopinavir-ritonavir and other HIV protease inhibitors except in a clinical trial setting (Strong recommendation based on RCT).

Summary of evidence on the clinical efficacy of remdesivir

Three RCTs provide inconsistent evidence of efficacy for remdesivir in COVID-19 (32-34). The largest of these was stopped early, following interim analysis showing benefit in time to recovery, while a smaller study reported no evidence of benefit compared with placebo, though it was under-powered to detect a significant effect (32, 34). Neither trial was powered to detect a difference in mortality between treatment groups. Nevertheless, the emerging evidence has formed the basis for a marketing authorisation application to the EMA in Europe and Emergency Use Authorisation by the FDA in the US. Results were announced in a press release from a fourth RCT, which has yet to be published.

An open-label RCT including 397 patients hospitalised with severe COVID-19 found no significant difference in efficacy between a 5-day course and a 10-day course of intravenous remdesivir treatment **(Goldman, 27/05/20)** (33). A clinical improvement of 2 points or more (on a 7-point ordinal scale consisting of severity categories ranging from 1=death to 7=not hospitalised) occurred in 65% of patients in the 5-day group and in 54% of patients in the 10-day group. Adjusting for differences in baseline disease-severity, distribution in clinical status was similar between groups. Time to clinical improvement was also similar between groups (10 days vs 11 days). The clinical relevance of the study findings are limited due to the lack of a control arm, and a limited existing evidence base supporting the efficacy of remdesivir compared with placebo or standard of care. Results cannot be extrapolated to critical disease as few patients were receiving mechanical

ventilation at the time of treatment initiation. The open-label design of the study is a recognised source of bias, particularly with regard to outcome assessment.

A preliminary report from a double-blind RCT of remdesivir in COVID-19 (ACTT-1 study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID, part of NIH)) published results from an interim analysis of 1,063 patients randomised 1:1 to receive either remdesivir or placebo for up to 10 days **(Beigel, 22/05/20)** (32). Most patients (88.7%) had severe disease at enrolment. Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days vs 15 days; rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). Benefit was most pronounced for patients with an ordinal score of 5 at baseline (i.e. requiring supplemental oxygen) (rate ratio for recovery 1.47, 95% CI, 1.17 to 1.84), likely due to the large sample size in this category. Mortality was numerically lower in the remdesivir group than in the placebo group by day 14, but the difference was not significant (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04; 1,059 patients). Serious adverse events occurred in 21.1% and 27.0% of patients in the remdesivir and placebo groups, respectively. The interpretation of mortality data from this study is limited by the large number of patients yet to complete the study. Even with complete follow-up, the ability of the trial to demonstrate a mortality benefit from treatment is hampered by the early unblinding of treatment assignment and the facility to discontinue placebo (32).

On the basis of preliminary results from the ACTT-1 study, the EMA completed a rolling review of data on the use of remdesivir to treat COVID-19 on 15 May 2020 and has received an application for a conditional marketing authorisation for remdesivir(35).

One investigator-initiated RCT **(Wang, 29/04/20)**, conducted in 237 patients in China, has published disappointing findings for remdesivir, reporting no evidence of benefit compared with placebo in the time to clinical improvement within 28 days (34). Patients received 200 mg remdesivir by intravenous infusion on day 1 followed by 100 mg on days 2 to 10, or placebo infusions for 10 days. The time to clinical improvement in the remdesivir group was not significantly different to that of the placebo group (median 21.0 days vs 23.0 days, HR 1.23, 95% CI 0.87 to 1.75). No difference was observed in 28-day mortality between the two groups (14% in the remdesivir group vs 13% in the placebo group; difference), or other secondary endpoints. The authors reported a numerical improvement in time to clinical improvement in the subgroup of patients receiving remdesivir within 10 days of symptom onset, though this was not statistically significant, and the study was not powered to detect a difference in this subgroup. The study is limited by its failure to enrol an adequate pre-defined sample size, resulting in an underpowered trial which may not be capable of demonstrating an effect, if one exists. More patients in the remdesivir group than the placebo group discontinued the study drug because of adverse events or serious adverse events (12% vs 5%). The patient population had less severe disease than other published cases treated with remdesivir - most patients (82%) required supplemental oxygen but not high-flow or mechanical

ventilation. The duration of symptoms prior to starting treatment (11 days) was longer than is expected in other ongoing clinical trials of remdesivir.

Top line results from the Phase III **SIMPLE trial** in hospitalized patients with moderate COVID-19 pneumonia, reported that a 5-day course of remdesivir resulted in significantly greater clinical improvement versus treatment with standard of care alone (36). At day 11, an improvement of ≥2 points in the ordinal scale was observed in 70%, 65% and 61% of patients treated with 5-day remdesivir, 10-day remdesivir and standard of care, respectively. Results were reported as favourable, trending toward but not reaching statistical significance for 10-day remdesivir. Publication of full study reports is awaited.

In a case series reporting data for 53 patients with severe COVID-19 (median age 64 years, 75% male, 64% receiving invasive ventilation) **(Grein, 10/04/20)**, remdesivir was initiated at a dose of 200 mg IV on day 1, followed by 100 mg daily up to day 10 (37). The median duration of symptoms before treatment initiation was 12 days. During a median follow-up of 18 days, seven patients (13%) died. Mortality was 18% (6/34) among patients receiving invasive ventilation and 5% (1/19) among those not receiving invasive ventilation. Thirty-six patients (68%) had an improvement in the category of oxygen-support. Twelve patients (23%) had serious adverse events. Viral load data were not collected. The case series excluded eight patients for whom post-baseline data were missing. Interpretation of the results of this study is limited by the lack of a control group, the short duration of follow-up and the high degree of missing data. Evidence for the clinical efficacy and safety of remdesivir is awaited from the publication of results of completed and ongoing clinical trials.

Summary of consensus guidelines on remdesivir

Infectious Diseases Society of America (updated 22/06/2020) (22)	• Among hospitalised patients with severe COVID-19, remdesivir is suggested over no antiviral treatment (Conditional recommendation, Moderate certainty of evidence) • Among patients with severe COVID-19 on supplemental oxygen but not on mechanical ventilation or ECMO, treatment with remdesivir is suggested for five days rather than 10 days. In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.
American Thoracic Society (updated 03/04/2020) (23)	No suggestion for or against remdesivir for hospitalised patients who have evidence of pneumonia, due to unknown adverse effect profile and uncertainty regarding timing of initiation and duration.

Surviving Sepsis Campaign (updated 28/03/2020) (24)	Insufficient evidence to issue a recommendation on the use of "other antiviral agents" in critically ill adults with COVID-19
National Institutes of Health (NIH, updated 12/05/20) (25)	• Insufficient data to recommend for or against use in mild or moderate COVID-19 • Recommended in hospitalised patients with severe disease (SpO_2 ≤94% on ambient air or require supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation) (Moderate recommendation based on RCT) • Duration of 5 days recommended for patients who are not intubated. Insufficient data on the optimal duration for mechanical ventilated patients, patients on ECMP, or patients who have not shown adequate improvement after 5 days. In these groups, some experts extend the total treatment duration up to 10 days (Optional recommendation based on expert opinion)

Rapid Evidence Review

Background

On the basis of preliminary antiviral prioritisation recommendations by the World Health Organisation, a targeted literature search (See Appendix 1 for the Search Strategy) was developed to identify clinical studies reporting the efficacy of hydroxychloroquine/chloroquine, lopinavir-ritonavir and remdesivir for the treatment of COVID-19 (38, 39). The Evidence Review Group (ERG) repeats the literature search twice weekly and completes a rapid critical appraisal of relevant studies. A landscape analysis of consensus clinical guidelines and international recommendations from WHO and EMA is also conducted. A summary of international, country-specific guidelines was included in previous versions of this review, but given the lack of recent updates to these guidelines and the emergence of international consensus guidelines, these have now been removed. Emerging evidence on other therapeutic candidate antivirals is also reviewed and summarised. Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or "preprints". These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.

Evidence for the clinical efficacy of hydroxychloroquine for COVID-19

Hydroxychloroquine is an antimalarial drug with several pharmacological actions which impart therapeutic efficacy primarily in the treatment of rheumatic disease (40). Hydroxychloroquine shares a similar chemical structure and mechanisms of action to chloroquine. Hydroxychloroquine (Plaquenil®) is licensed for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight (40). It is unlicensed for the treatment of COVID-19. At the time of writing, hydroxychloroquine is more readily accessible than chloroquine in Ireland (41). These drugs have been the focus of intense investigation and widespread anecdotal use since the beginning of the COVID-19 outbreak. They have the benefit of (historically) widespread availability, established safety profile in specific patient populations, and low cost. Effective in vitro inhibition of SARS-CoV-2 has been shown by hydroxychloroquine and chloroquine in pre-clinical studies (42, 43), and a number of sources have identified these drugs as potentially effective treatments for COVID-19 (44, 45). However, while many clinical trials are ongoing, a limited number of completed trials investigating the comparative efficacy of hydroxychloroquine have been published (3-5, 15, 16). In addition, safety concerns, in particular cardiac safety, arising from the specific use of

hydroxychloroquine or chloroquine for COVID-19, alone or in combination, have arisen (46-49). *Note: a separate Rapid Evidence Review specifically focussing on the efficacy of hydroxychloroquine/azithromycin combination therapy for COVID-19 has been published by the COVID-19 ERG (50).*

Clinical studies of hydroxychloroquine

Seventeen full study reports, one press-release and one study abstract, reporting the comparative efficacy of hydroxychloroquine for the treatment of COVID-19, were identified (3-5, 10-21, 51) (2, 9). A press-release announced preliminary results of the RECOVERY study, a large randomised, open-label study, with data from 1542 patients randomised to hydroxychloroquine compared with 3132 patients randomised to usual care alone (2). Two small RCTs, one double-blind, one open-label, were conducted in 62 patients and 150 patients, respectively. Both RCTs were conducted in China and described the efficacy of hydroxychloroquine plus SoC compared with SoC alone (3, 4). An open-label, non-randomised clinical trial of hydroxychloroquine compared with a control group was conducted in 42 patients in France (15). Ten retrospective cohort studies compared patients who received hydroxychloroquine with a concurrent control cohort who did not receive hydroxychloroquine (10-14, 16-18, 52) (9). A third RCT, available only as an abstract in English, reported the outcomes of 30 treated with hydroxychloroquine compared with a control group (5). Three other non-comparative case-series reports, on the use of hydroxychloroquine in combination with azithromycin, were also identified (19-21). Comparison between studies and formal meta-analysis are limited by significant heterogeneity in study design, outcome definitions, interventions and controls. A systematic review of clinical trials of hydroxychloroquine and chloroquine for COVID-19 recently concluded that quantitative analysis was not possible. All trials identified in the review were judged to have serious methodological flaws (53).

Randomised controlled trials

RECOVERY TRIAL, 05th June 2020 (Press-release of preliminary results)

RECOVERY is a randomised, open-label trial investigating whether treatment with either lopinavir-ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevents death in patients hospitalised with COVID-19 (54). The primary outcome is all-cause mortality within 28 days after randomisation. Preliminary results of a review by the independent Data Monitoring Committee reported data from 1542 patients randomised to hydroxychloroquine and 3132 patients randomised to usual care alone (2). There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; HR 1.11 95% CI 0.98-1.26; p=0.10). There was also

no evidence of beneficial effects on hospital stay duration or other outcomes. Enrolment into to the hydroxychloroquine arm of the trial has been stopped (2).

A full critical appraisal of this study is not possible in advance of publication of the full study results. However, details available in the full trial protocol indicate the potential for a well-conducted trial, capable of delivering robust results. The high mortality rate indicates a severe cohort of patients, suggesting that the results may not be applicable to patients with mild/moderate COVID-19.

WHO SOLIDARITY TRIAL, 17th June 2020 (Press-release)

A press release from the **WHO SOLIDARITY trial (17/06/20)** announced that data showed that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care. The principal investigators have stopped the hydroxychloroquine arm of the study, based on evidence from the Solidarity trial, UK's Recovery trial and a Cochrane review of other evidence on hydroxychloroquine (55).

Tang W et al. 14th May 2020 (Peer-reviewed RCT report, first appeared as a preprint on April 14th (version 1) and 07th May (version 2))

Tang et al conducted a multicentre, open-label RCT to assess the efficacy and safety of hydroxychloroquine in adult patients with COVID-19 (4). One hundred and fifty patients hospitalised with COVID-19 were enrolled across 16 government-designated COVID-19 treatment centres in China between 11th and 29th of February 2020 (4). Seventy-five patients were assigned to hydroxychloroquine plus SoC and 75 were assigned to SoC alone (control group). The dose of hydroxychloroquine was 1200 mg daily for three days followed by a maintenance dose of 800 mg daily for a total treatment duration of two or three weeks for mild/moderate or severe patients, respectively. SoC in the trial could have included other potential antiviral therapies. The primary endpoint was the negative conversion of SARS-CoV-2 within 28 days. An earlier version 1 of this paper reported on the alleviation of symptoms, described as a key secondary endpoint. However, results for this outcome were removed in version 2 of the report as the trial was stopped early and only two patients with severe disease had been enrolled. The mean age of the cohort was 46 years and 55% were male. Thirty per cent of the cohort had pre-existing conditions. There were some imbalances between treatment groups in the proportions of patients with pre-existing conditions (37.3% in the hydroxychloroquine group vs 22.7% in the SoC group), and in the proportions with mild/moderate disease (20%/78.7% in the hydroxychloroquine group vs 9.3%/89.3% in the SoC group). The mean duration from disease onset to randomisation was 16.6 days. The majority of the patients had mild to moderate COVID-19 (99%) and only 2 patients (1%) had severe COVID-19 at screening. The negative conversion rate of SARS-CoV-

2 was similar between treatment groups: 85.4% (95% CI 73.8% to 93.8%) in the hydroxychloroquine/SoC group vs 81.3% (95% CI, 71.2% to 89.6%) in the SoC group. There was no difference in time to negative conversion (median 8 days vs. 7 days; HR 0.846; 95%CI 0.580 to 1.234; P=0.341). There was no significant difference in the rate and time to alleviation of clinical symptoms, although a non-significant greater reduction in CRP and a more rapid recovery of lymphopenia was observed. A significantly higher proportion of patients in the hydroxychloroquine group reported adverse events (30% vs 8.8%). The most common adverse event in the hydroxychloroquine recipients was diarrhoea (10%).

The study is limited by the duration of time from illness onset to randomisation (16.6 days), though the authors comment that findings were similar in a subgroup of patients who received treatment within seven days of illness onset. Other potential antiviral therapies were permitted as part of SoC including lopinavir-ritonavir, arbidol, oseltamivir, virazole, entecavir, ganciclovir and/or interferon-alpha. As the efficacy of these agents for COVID-19 is as yet unproven, it is not possible to determine what bias may have been conferred on the study from the use of these concomitant therapies(4).

Chen Z et al. 30th March 2020 (RCT report, Preprint)

Chen et al reported on a randomised, controlled double-blind study conducted at the Renmin Hospital of Wuhan University (Wuhan, China) on March 30th 2020 (3). Sixty-two hospitalised patients with COVID-19 who met inclusion criteria were randomised 1:1 to receive standard treatment alone (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids) or standard treatment plus hydroxychloroquine 400 mg daily for five days. Patients with confirmed SARS-CoV-2were included if they were ≥18 years, had pneumonia on chest CT, and had mild respiratory illness (SaO2/SPO2 ratio > 93% or PaO_2/FIO_2 ratio > 300 mmHg). Exclusion criteria included severe or critical illness, retinopathy or other retinal diseases, arrhythmias, among others (3). Clinical characteristics and radiological results were assessed at baseline and 5 days after treatment initiation. The primary endpoint was time to clinical recovery (TTCR), defined as the return of body temperature and cough relief, maintained for more than 72 hours. The mean age of patients was 44.7 years, and 46.8% were male. No details were provided on baseline distribution of co-morbidities known to be associated with poorer outcomes in COVID-19, such as chronic respiratory and cardiovascular disease. 22/31 and 17/31 patients had a fever before the intervention in the hydroxychloroquine and control groups, respectively. 22/31 and 15/31 patients had a cough before the intervention in the hydroxychloroquine and control groups, respectively. The times to fever recovery and cough recovery were approximately one day shorter in the hydroxychloroquine group (fever: 2.2 (SD 0.4) days vs 3.2 days (SD 1.3), p=0.0008; cough: 2.0 (SD 0.2) days vs 3.1 (SD 1.5) days, p=0.0016). Four patients, all in the control group progressed to severe illness. Improvement in pneumonia, assessed by chest CT, occurred in 25/31 patients (80.6%) in the hydroxychloroquine group compared with 17/31 (54.8%) in the control group (3).

This study is limited to patients with mild COVID-19 disease, and has a very short (five-day) follow-up. Limited details of standard-care received by patients were provided e.g. the nature of other antivirals or antibiotics which may have been received. Interpretation of the findings is further limited by the absence of detail on the balance, or otherwise, across treatment groups in important prognostic factors such as baseline comorbidities (3).

Chen J et al. 06th March 2020 (RCT Abstract)

An English abstract of a Chinese study reporting the use of hydroxychloroquine in China was published on 6th March 2020 (5). Thirty, treatment-naïve, patients with confirmed COVID-19 were randomised 1:1 to hydroxychloroquine 400mg daily for five days, or a control group. The disease status of the patients at enrolment was not reported, though it is assumed that they were not severe. The primary endpoint was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab after seven days. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (P>0.05). Similarly, no differences were observed between the treatment groups in median time for body temperature normalization median duration from hospitalization to virus nucleic acid negative conservation. A lower proportion of patients had radiological progression shown on CT (5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group).

Patient numbers and effect sizes in this study are too small to robustly determine a difference in efficacy between treatment groups. Insufficient information is available to critically appraise the quality of the study (5).

Observational studies

Sbidian et al. 19th June 2020 ((Retrospective cohort study, Preprint)

A retrospective cohort study assessed the clinical effectiveness of oral HCQ in preventing death or allowing hospital discharge using the Corona OMOP database, which combines electronic medical records and administrative claim data from 39 hospitals in France. Hydroxychloroquine- and azithromycin-naïve, adult inpatients with confirmed SARS-CoV-2 were eligible for the analysis. Patients receiving other specific, investigational COVID-19 treatments were excluded. The primary and secondary outcomes were all-cause 28-day mortality, and 28-day discharge home, respectively, both assessed as time-to-event endpoints. Patients were classified into three groups: (i) receiving hydroxychloroquine alone, (ii) receiving hydroxychloroquine together with azithromycin, and (iii) receiving neither hydroxychloroquine nor azithromycin. A Cox proportional hazards regression model was constructed to account for the competing risk between all-cause death and hospital discharge. Confounding due to interaction between treatment assignment and baseline

covariates, was accounted for using augmented inverse probability of treatment weighting (AIPTW) estimators of average treatment effects (ATE), derived using propensity scores. 4,642 patients (mean age: 66.1 years; 59% males) were included in the study population, of whom 623 (13.4%) received hydroxychloroquine alone, 227 (5.9%) received hydroxychloroquine+azithromycin, and 3,792 (81.7%) neither hydroxychloroquine nor hydroxychloroquine+azithromycin. Patients receiving hydroxychloroquine, either alone or in combination with azithromycin, were more likely to be younger, male, current smokers, compared with the "Neither drug" group. Co-morbidities were slightly more also common in hydroxychloroquine-treated, including obesity, diabetes, any chronic pulmonary diseases, liver diseases. Biological parameters were similar across groups. There were significant differences in 28-day mortality rates (17.8%-23.8%) and discharge rates at day 28 (39.7%-56.3%) across groups. However, after accounting for confounding: no statistically significant difference was observed between the 'hydroxychloroquine' and 'Neither drug' groups for 28-day mortality: AIPTW absolute difference in ATE was +1.24% (-5.63 to 8.12), ratio in ATE 1.05 (0.77 to 1.33). 28-day discharge rates were statistically significantly higher in the 'hydroxychloroquine' group: AIPTW absolute difference in ATE (+11.1% [3.30 to 18.9]), ratio in ATE (1.25 [1.07 to 1.42]). For the 'hydroxychloroquine+azithromycin' group vs. 'Neither drug' comparison, a trend was found towards higher mortality rates in the 'hydroxychloroquine+azithromycin' group, though not reaching statistical significance (difference in AIPTW ATE +9.83% [-0.51 to 20.17], ratio in ATE 1.40 [0.98 to 1.81]; p=0.062). Results were robust to a variety of sensitivity analyses.

This study is limited by its retrospective, observational design. Advanced methods of adjustment for confounding were applied, in addition to several sensitivity analyses which supported the stability of results. Direct indicators of disease severity such as respiratory parameters were lacking; though biological parameters were used as proxies. Findings may only be applicable to a hospitalised cohort of patients with COVID-19 and cannot be extrapolated to patients with milder disease.

Ip et al. 25th May 2020 (Retrospective cohort study, Preprint)

A retrospective, observational, multicentre cohort study analysed data from the electronic health records of 2,512 patients hospitalised with COVID-19 within a 13-hospital network in the US (10). A convenience sample of 97% of available records was abstracted. Patients enrolled in clinical trials, and those who died or were discharged within 24 hours, were excluded. Four treatment groups were defined: 1) Hydroxychloroquine n=441, 2) Hydroxychloroquine in combination with Azithromycin n=1473, 3) Azithromycin alone n=256, and 4) neither drug n=342. The association between tocilizumab-exposure and clinical outcomes was also investigated as part of this study. The primary outcome measure was death with follow-up through May 5, 2020. A Cox proportional hazards model was used, with propensity-score stratification to adjust for potential confounders arising from

observed imbalances across treatment groups. The model for selecting factors to be included in propensity scores was a two-stage backward selection approach, considering the following factors for inclusion: gender, coronary disease, stroke, heart failure, arrhythmia, African American, COPD, renal failure, rheumatologic disorder, inflammatory bowel disease, advanced liver disease, age, diabetes mellitus, insulin use prior to hospitalisation, asthma, HIV/hepatitis, any cancer, and log ferritin. Propensity scores were stratified into quintiles and used as an ordinal variable to adjust the relative treatment comparison in the Cox model. The median age of the cohort was 64 years and 62% were male. Hypertension, obesity and diabetes were observed in 55%, 41%, and 32% of the cohort respectively. 31% of the cohort had three or more chronic conditions. The median time from symptom-onset to hospitalisation was 5 days (IQR 3-7). Sp02 was <94% in 44% of patients and 24% required ICU support during their hospitalisation. Significant differences in disease severity and baseline comorbidity were observed between patients receiving hydroxychloroquine at any stage and patients who did not receive hydroxychloroquine. However, baseline characteristics according to individual treatment group were not provided. The majority of patients treated with hydroxychloroquine received a dose of 800mg on day 1 followed by 400mg on day 2-5 (80%), for a median duration of 5 days. Discontinuation of hydroxychloroquine due to prolongation of QTc or arrhythmias occurred in 5% of patients. The unadjusted 30-day mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, respectively. There was no significant association between survival and any use of hydroxychloroquine during the hospitalisation (adjusted HR 0.99. 95% CI 0.80-1.22]), hydroxychloroquine alone (HR 1.02, 95% CI 0.83-1.27), or hydroxychloroquine in combination with azithromycin (HR 0.98, 95% CI 0.75-1.28). Tocilizumab demonstrated a trend towards reduced mortality among ICU patients.

It was not possible to discern differences in baseline characteristics between groups as this data was not provided. Although propensity modelling was used to mitigate observed imbalances across treatment groups, the extent of these imbalances is not clear, and it is possible that unmeasured confounding factors may still be present. Dosing and timing of hydroxychloroquine varied throughout the hospital network. These factors were difficult to quantify in the study. Findings were limited to hospitalised patients. The study used a convenience sample for the purposes of conducting the investigation quickly, however the impact of convenience sampling is considered to be mitigated by the abstraction of the vast majority of the available data (97%).

Mehra et al. 22nd May 2020 (Retracted 04th June 2020, peer-reviewed, retrospective cohort study)

**This study was a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for the treatment of COVID-19, comprising data from 96,032 patients in 671 hospitals across six continents (6). External expressions of*

*concern regarding statistical analysis and data integrity led three of the authors of this study to commission an independent third-party peer-review of the corporation who conducted the data analysis (7, 56). On 04th June 2020, these authors requested that the paper be redacted as they can no longer vouch for the veracity of the primary data sources (8).**

Kim et al. 18th May 2020 (Retracted 14th June, retrospective cohort study, Preprint)

**This study was a retrospective cohort study in a hospital in Korea comparing responses in a subgroup of 97 patients with moderate COVID-19 to various treatments, including hydroxychloroquine, lopinavir-ritonavir, or conservative treatment (52). The authors have withdrawn this manuscript because of the controversy about hydroxychloroquine and potential changes in results after peer-review. The authors intend to share their results in formal publication and do not wish this work to be cited as reference for the project (57). **

Mahevas et al. 14th May 2020 (Retrospective cohort study, Preprint) (Peer-reviewed Retrospective cohort study report, first appeared as a preprint on April 14th2020)

Data collected from all adult patients with SARS-CoV-2 pneumonia and requiring oxygen by mask or nasal prongs, treated in four French hospitals between March 12th and 31st 2020, were retrospectively analysed to assess the efficacy of hydroxychloroquine compared with a control (no hydroxychloroquine) group. Eighty-four patients received hydroxychloroquine and 97 patients, from the same treatment centres who did not receive hydroxychloroquine, served as a concurrent control cohort (16). Patients were treated with hydroxychloroquine 600mg daily within 48 hours of hospitalisation, or not treated with hydroxychloroquine during this two-day period (control group). Eight of the patients in the control group did receive hydroxychloroquine later on during their admission, and these patients were excluded from the main, per-protocol analysis. The primary outcome was survival without transfer to the intensive care unit at day 21. Secondary outcomes were overall survival, survival without ARDS weaning from oxygen, and discharge from hospital to home or rehabilitation (all at day 21). ECGs were conducted prior to treatment initiation and for 3-5 days afterwards. An inverse probability of treatment weighting (IPTW) approach was used to balance the differences in baseline variables between treatment groups. A propensity score model was used, based on prespecified covariates including age; gender; comorbidities; BMI; third trimester of pregnancy; treatment with ACE inhibitors or ARBs; time since symptom onset; severity of disease; presence of confusion; respiratory frequency; oxygen saturation without oxygen; oxygen flow; systolic blood pressure; and CRP. Sensitivity analyses were conducted to assess the robustness of findings, using different analytical methods and excluding patients who started hydroxychloroquine more than 48 hours after admission. After applying IPTW, 15 of the 19 covariates in the planned propensity score had weighted standardised differences below 10% while four exceeded the threshold and were not included in the final propensity score model (confusion at

admission, and three specific co-morbidities: chronic kidney disease, heart failure and liver cirrhosis, were present in only 0 of 1 patient in the hydroxychloroquine group). The median age of the cohort was 60 years, and 72% were men. Patients in the treatment group had fewer comorbidities, except for liver cirrhosis. Initial severity was well balanced between the groups, except for confusion on admission which was observed in 6 patients in the control group and none in the treatment group. The median interval between symptom onset and hospital admission was 7 days. Azithromycin was administered to 18% of the participants in the treatment group versus 29% in the control group; amoxicillin and clavulanic acid was given to 52% versus 28%, respectively (excluding co-interventions in patients transferred to the intensive care unit). The overall survival rate at day 21 was 89% in the treatment group and 91% in the control group (1.2, 0.4 to 3.3). In the weighted analyses, the survival rate without transfer to the ICU at day 21 was 76% in the treatment group and 75% in the control group (weighted HR 0.9, 95% confidence interval 0.4 to 2.1). Survival without ARDS at day 21 was 69% in the treatment group compared with 74% in the control group (1.3, 0.7 to 2.6). SARS-CoV-2 PCR was not followed up in this study. Sensitivity analyses provided consistent results. Eight patients (9.5%) receiving hydroxychloroquine discontinued treatment due to ECG changes at a median of four days after treatment initiation.

This study is limited by its retrospective nature and the lack of randomisation to treatment groups which is associated with an increased potential for unmeasured confounders to bias results. A centre effect could not be accounted for as some centres treated all patients with hydroxychloroquine while others did not. The possibility for SoC to differ across centres and impact differentially on clinical outcomes cannot be excluded.

Rosenberg et al. 11th May 2020 (Peer-reviewed, retrospective cohort study)

A retrospective cohort study across 25 hospitals in New York State included a random sample of all admitted patients with laboratory-confirmed COVID-19 (12). Eligible patients were admitted for at least 24 hours between March 15 and 28, 2020. The date of final follow-up was April 24, 2020. Patients were categorised into groups based on treatment during hospitalisation: (1) hydroxychloroquine with azithromycin, (2) hydroxychloroquine without azithromycin (hydroxychloroquine alone), (3) azithromycin alone, and (4) neither drug. The primary outcome was in-hospital mortality, with additional secondary outcomes of cardiac arrest and abnormal electrocardiographic findings. A Cox proportional hazards model was fit for time to death, controlling for treatment group and potential confounders (age ≥65 years, sex, hospital, diabetes, chronic lung disease, CVD, respiratory rate >22/min, O_2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels). 1438 patients were included in the analysis. Of these patients, 735 (51.1%) received hydroxychloroquine+azithromycin, 271 (18.8%) received hydroxychloroquine alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither drug. The median age across treatment groups was 61.4-65.5 years. There were differences between treatment group in baseline demographics, including gender (49.8%-63.5% male), obesity,

and co-morbidities. Patients receiving either drug were more likely to be male. Patients receiving hydroxychloroquine alone had the highest levels of chronic lung disease (25.1%) and CVD (36.5%). Patients in treatment groups had more clinically severe disease than the neither drug group. Patients receiving hydroxychloroquine, alone or in combination, had higher levels of ICU admission and mechanical ventilation. Overall in-hospital mortality was 20.3%. In unadjusted analyses, significant differences in in-hospital death were observed across groups. However, following adjustment for potential confounders, no significant differences in mortality were found between patients receiving hydroxychloroquine+azithromycin (adjusted HR 1.35, 95% CI 0.76 to 2.40), hydroxychloroquine alone (adjusted HR 1.08, 95%CI 0.63 to 1.85), or azithromycin alone (adjusted HR 0 .56, 95% CI 0.26 to 1.21), compared with the neither drug group. No significant mortality difference was found between hydroxychloroquine alone and azithromycin alone (adjusted HR, 1.92, 95% CI 0.99 to 3.74). Results were similar using three alternative Cox models. In logistic regression models of abnormal ECG findings, there were no significant differences between the groups receiving neither drug and each of the hydroxychloroquine+azithromycin and hydroxychloroquine alone groups. However, cardiac arrest was more likely in patients receiving hydroxychloroquine+azithromycin compared with those receiving neither drug (adjusted OR 2.13 95% CI, 1.12 to 4.05; E-value = 1.31) (12).

This study is limited by its retrospective, observational design. Mortality was limited to in-hospital death with the assumption that discharged patients were still alive at the end of the study-period. The association between adverse events and the timing of treatment initiation is unknown. Although appropriate statistical methods were used to attempt to reduce the potential effects of confounding, unmeasured residual confounding in the analysis cannot be excluded.

Carlucci et al. 08th May 2020 (Retrospective cohort study, Preprint)

A retrospective analysis of data from patients hospitalised with confirmed SARS-CoV-2 infection at four New York hospitals, compared outcomes among patients who received hydroxychloroquine and azithromycin plus zinc (n=411) versus hydroxychloroquine and azithromycin alone (n=521) (17). Only patients who had been discharged, transitioned to hospice or died were included. It is not explicit in the study report but it appears as if patients who remained in hospital were not included. Numerous outcomes were investigated, but no primary outcome was specified. While the baseline demographics of the treatment groups appeared to be balanced, the analysis is confounded by timing, given that hospital policy changed mid-follow-up from hydroxychloroquine and azithromycin alone, to hydroxychloroquine and azithromycin plus zinc. After adjusting for timing, the authors found that the addition of zinc sulfate to hydroxychloroquine and azithromycin was associated with a decrease in mortality or transition to hospice among patients who did not

require ICU level of care, but this association was not significant in patients who were treated in the ICU (17).

The findings of this study have limited clinical relevance in the absence of a control arm comprising patients who did not receive hydroxychloroquine as the efficacy of this treatment, alone or in combination, has not been proven. This study is limited by its apparent exclusion of patients who remained in hospital at the end of study follow-up, and by the limited methods applied in the final analysis, which appears to only be adjusted for differences in timing.

Geleris et al. 07th May 2020 (Peer-reviewed, retrospective cohort study)

An observational study in a New York hospital studied the association between hydroxychloroquine use and intubation or death (11). At the time of the study, while treatment decisions were at the clinician's discretion, guidance in the hospital suggested hydroxychloroquine (at a dose of 600 mg twice daily on day 1 followed by 400 mg daily for 4 additional days) as a therapeutic option for patients with COVID-19 who presented with moderate-to-severe respiratory illness ($Sp0_2$ ≤94% on room air). Azithromycin 500 mg on day 1 and then 250 mg daily for 4 more days in combination with hydroxychloroquine was an additional suggested therapeutic option. Data on 1376 consecutive patients hospitalised with COVID-19 (excluding those who were intubated, died or discharged within 24 hours of study baseline) were analysed. The association between hydroxychloroquine use and the primary endpoint, time from study baseline to intubation or death, was estimated by multivariable Cox regression models, inverse-probability-weighted using propensity score methods. These methods were used to control for potential confounding associated with observational studies of this type. The Cox model was stratified according to sex, chronic lung disease, and BMI, with additional adjustment for age, race and ethnic group, insurance, current smoking, past diagnoses, current medications, vital statistics, and laboratory tests on presentation. Hydroxychloroquine was received by 811 patients, 85.9% of whom were treated within 48 hours, and 565 patients did not receive hydroxychloroquine. Azithromycin was received by 59.9% and 22.5% of patients in the hydroxychloroquine group and no-hydroxychloroquine group respectively. The median follow-up was 22.5 days. There were differences between treatment groups at baseline in disease severity (hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine, PaO_2:FiO_2 223 vs 360), and baseline medications. This is not unexpected, given the hospital guidance on hydroxychloroquine treatment. Overall, 346 patients (25.1%) had a primary end-point event (180 patients were intubated, of whom 66 subsequently died, and 166 died without intubation). In the primary multivariable analysis with inverse probability weighting according to the propensity score, there was no significant association between hydroxychloroquine use and intubation or death (HR 1.04; 95% CI, 0.82 to 1.32). There was also no significant association between treatment with

azithromycin and the composite end point (HR 1.03; 95% CI, 0.81 to 1.31). Results were similar in multiple sensitivity analyses, including different analytical methods (11).

Limitations of this study include the retrospective, observational, non-randomised design which introduces confounding and bias. The analytical methods used were appropriate to minimise the confounding and bias associated with non-randomised studies, however it is possible that some unmeasured confounding remains.

Mallat et al, 02nd May 2020 (Retrospective cohort study, Preprint)

A small, retrospective observational study analysed time to negative nasopharyngeal swab conversion in all patients with confirmed SARS-CoV-2 infection admitted to one hospital in Abu Dhabi (N=34). Multiple linear regression analysis was used to identify if HCQ was independently associated with the time to negativity test after adjusting for symptoms, pneumonia or oxygen therapy. 21 patients (61.8%) received hydroxychloroquine. The median age was 37 years, and 73.5% were male. Hydroxychloroquine-treated patients were younger, with lower levels of D-dimer compared to controls. Co-morbidities were also generally more frequent in the control group. The median time from onset of symptoms to hospital admission was 4 days. No patients were admitted to intensive care unit, required high flow oxygen therapy, non-invasive or invasive mechanical ventilation, and all of them were discharged alive from the hospital. The time to SARS-CoV-2 negativity test was significantly longer in patients who received HCQ compared to those who did not receive the treatment (17 [13-21] vs. 10 [4-13] days, p=0.023). HCQ treatment was independently associated with a longer time to negativity test after adjusting for potential confounders, suggesting a slower viral clearance. On day 14, only 11 patients among the 23 patients treated with HCQ had their SARS CoV- 2 tests turned negative compared to 10 patients among the 11 patients who did not receive HCQ treatment (47.8% vs. 90.9%, respectively, p=0.016). HCQ treatment did not result in improvement of inflammatory markers or lymphopenia.

This was a small study, of retrospective design and is subject to selection bias due to the non-random allocation to treatment. Although results were adjusted for confounding, this was limited to symptoms, pneumonia or oxygen therapy and didn't address the imbalances between treatment groups in baseline characteristics. The potential for unobserved confounders to be present and selection bias to remain also cannot be outruled.

Yu et al. 01st May 2020 (Retrospective cohort study, Preprint)

A retrospective analysis of 568 critically ill patients with COVID-19, identified 48 patients who received hydroxychloroquine (oral 200mg twice daily for 7-10 days) and 520 patients who did not receive hydroxychloroquine (14). Patients had confirmed SARS-CoV-2 infection and were critically ill, meeting one of the following criteria: respiratory failure needing

mechanical ventilation; 2) septic shock during hospitalisation; 3) other organ failures that required monitoring and treatment in an ICU. The primary endpoint was mortality. Cox regression analysis was performed, in an attempt to eliminate the influence of confounding. A multivariate model was adjusted for age, sex, history of hypertension, diabetes, coronary heart disease, COPD, oxygen saturation and baseline treatment drugs.

The median age of the cohort was 68 years, 63% were male. 96% of patients required oxygen therapy, while 62% of patients were on mechanical ventilation. There were some differences in the prevalence of comorbidities across groups with more patients with diabetes in the hydroxychloroquine group (25.0% vs 16.3%) and more patients with coronary heart disease in the control group (11.0% vs 4.2%). No other details are provided on the baseline status of patients such as signs and symptoms, laboratory results, or assessment of disease severity e.g. NEWS2. Other antiviral drugs (Lopinavir and Ritonavir, Entecavir hydrate, or Ribavirin) were used concomitantly by 41.7% and 44.4% of patients in the HCQ and NHCQ groups, respectively. Interferon was used in none of the HCQ-treated patients, and 10.4% of the no-HCQ treated patients. Mortality was 45.8% (235/520) in the no-HCQ group and 18.8% (9/48) in the HCQ group (adjusted HR 0.32, 95% CI 0.16 to 0.62: p<0.001). In those that died, length of stay in hospital was longer in the HCQ group than the no-HCQ group (15 days vs 8 days, p=0.021). Levels of IL-6 decreased significantly from baseline in the HCQ-group but changed very little in the no-HCQ group. An increase in IL-6 levels was observed in the HCQ-group after treatment discontinuation. The authors postulate that the mechanism by which hydroxychloroquine may improve mortality in critically ill COVID-19 patients may be mediated through its inhibition of inflammatory cytokine storm on top in addition to a viral replication inhibitory effect (14).

This was a retrospective study, limited by potential selection bias and lacking the patient numbers in the hydroxychloroquine arm to appropriately adjust for the numerous covariates included in the multivariate model. While the groups appear to be somewhat well-balanced with some exceptions, key details on disease severity and laboratory results for this critically ill cohort are missing. The potential for unobserved differences to exist cannot be excluded in a non-randomised study. No reasons were provided for why some patients were treated with hydroxychloroquine and others were not. The impact on clinical outcomes from other antiviral drugs, which were used concomitantly during the trial, is unknown.

Magagnoli et al. 21st April 2020 (Retrospective cohort study, Preprint)

A retrospective analysis of data from patients hospitalized with confirmed SARS CoV-2 infection in all United States Veterans Health Administration medical centres up to April 11, 2020, was conducted (13). Available data included inpatient, outpatient, laboratory and pharmacy claims data. Patients were treated with hydroxychloroquine alone (HC, n=97), hydroxychloroquine and azithromycin (HC/AZ, n=113) or no hydroxychloroquine (no

HCn=158). The median age of the cohort was 68-70 years. All patients included in the analysis were male. Baseline demographic characteristics were similar; however HC and HC/AZ were more likely to be prescribed to patients with more severe disease, as assessed by baseline ventilatory status and metabolic and hematologic parameters. There were 27 deaths (27.8%) in the HC group, 25 deaths (22.1%) in the HC/AZ group, and 18 deaths (11.4%) in the no HC group. Mechanical ventilation occurred in 13.3% of the HC group, 6.9% of the HC/AZ group, and 14.1% of the no HC group. To account for differences in population characteristics, propensity scores for use of specific treatments were calculated based on all baseline characteristics. Compared to the no HC group, there was a higher risk of death from any cause in the HC group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC/AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72) (Table 5). There was no significant difference in the risk of ventilation or in the risk of death after ventilation in either the HC group or the HC+AZ group, compared to the no HC group.

This study is limited by its retrospective nature and the lack of a prospectively assigned, randomised control arm. This resulted in selection bias, with more severe disease in the active treatment groups. The differences in mortality observed between groups persisted when controlling for baseline characteristics using propensity score methods, however limited detail of the propensity score adjusted analysis were provided. The study relates only to men, with a median age of 65 years. 31.7% of the No-HC group received azithromycin. Azithromycin has been suggested to have antiviral activity in its own right, though this is unproven (13).

Gautret et al. 20th March 2020 (Peer-reviewed, observational study report)

In an open-label, non-randomised clinical trial, co-ordinated by the IHU Méditerranée Infection in Marseille, the effect of hydroxychloroquine compared with a control group was investigated in 42 hospitalised patients with SARS-CoV-2 infection (15). The mean time between onset of symptoms and study inclusion was 4.1 days in the treatment group. Not all patients were symptomatic at the time of treatment initiation. Twenty-six patients received hydroxychloroquine sulfate 200mg three times daily for ten days. Sixteen untreated patients from another centre and cases refusing the protocol were included as negative controls. These 16 control patients did not receive hydroxychloroquine. Six hydroxychloroquine-treated patients (23%) were reported as lost to follow-up (three due to transfer to an intensive care unit, one due to death, one due to nausea and one due to patient decision to discharge from hospital). Among hydroxychloroquine patients, six patients received azithromycin (500mg on day one, followed by 250mg per day for the next four days) to prevent bacterial super-infection. The criteria for selecting patients for combination treatment with hydroxychloroquine-azithromycin were not reported. It was not reported if any of the control patients received azithromycin. Hydroxychloroquine patients were older than control patients (51.2 years vs 37.3 years). Two (10%) of the hydroxychloroquine patients and four (25%) of the control patients were asymptomatic. An

intention-to-treat analysis was not undertaken, as the patients who were lost-to-follow-up were not included in the efficacy analyses. The authors reported that 70% (14/20) of the hydroxychloroquine-treated patients were virologically cured compared with 12.5% (2/16) in the control group (p=0.001) at day six post-inclusion. The patients who were lost-to-follow-up were not included in the efficacy analyses. Under the assumption of treatment failure among those who are lost-to-follow-up, 54% (14/26) were virologically cured. All six patients treated with hydroxychloroquine-azithromycin were virologically cured at 6 days however one patient who met the primary outcome of virological clearance at day 6 tested positive again at low titre at day 8.

A number of limitations were identified. Patients were not randomised to treatment and the methods used to identify and select patients for each treatment arm were not described by the authors. This is a particular concern for the control group which included patients who refused the treatment or who were treated in other centres. This study is therefore at high risk of selection bias. There were also some differences in the baseline characteristics of each treatment arm. Hydroxychloroquine patients were older than control patients (51.2 years vs 37.3 years). Two (10%) of the hydroxychloroquine patients and four (25%) of the control patients were asymptomatic. The authors reported that "Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients", though this data was not provided. Further the exclusion of six patients as lost to follow up, given the known outcome introduces considerable bias in the determination of response.

Case-series

Million et al. 20th April 2020 (Case series, Preprint)

A third report, from the investigators at the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection in Marseille, reported clinical and virological outcomes of 1061 patients treated with hydroxychloroquine-azithromycin combination (21). Patients were identified following early unrestricted PCR screening for in people with suspected COVID-19 and asymptomatic contacts of confirmed cases between March 3rd and 31st 2020. Individuals with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample were offered hydroxychloroquine 200mg three times daily for ten days combined with azithromycin 500mg on day 1 followed by 250mg mg daily up to day 5, on an outpatient or inpatient basis, as required. The primary outcomes were i) an aggressive clinical course requiring oxygen therapy, transfer to the ICU or death after at least three days of treatment, and prolonged hospitalization (10 days or more), and ii) contagiousness as assessed by PCR and culture. In total, 3165 patients managed at IHU tested positive for COVID-19. The case series analysis included 1061 patients who received at least three days of treatment and eight days of follow-up. Reasons for exclusion were provided for 350 patients, including 33 with cardiac contraindications and 15 with potential risk for drug interactions. No details

were provided on the remaining cohort of patients who tested positive but weren't included in the analysis. The mean age of included patients was 43.6 years, and 46.4% were male. The mean time between symptom onset and treatment initiation was 6.4 days (SD 3.8). Chronic respiratory diseases were present in 10.5%, hypertension in 14% and diabetes in 7.4% of the cohort, among other co-morbidities. The vast majority of patients (95%) had a low NEWS score (0-4) and 34.3% had normal pulmonary CT within 72 hours of admission. The study does not provided details on presence/absence/spectrum of symptoms, or on the proportions of patients who were hospitalised or treated as outpatients. A poor clinical outcome (death or transfer to ICU or hospitalization for 10 days or more) was observed for 46 patients (4.3%) and eight patients died (0.75%). The authors identified that mortality rates were lower in this cohort compared with other settings, suggesting that this may be attributable to the use of the hydroxychloroquine-azithromycin combination. However the methods of comparison were crude and not robust. Forty-seven patients (4.4%) exhibited a persistent nasal viral carriage at completion of treatment. ECGs were performed at baseline; however the study makes no further reference to safety or adverse events. The study abstract stated that no cardiac toxicity was observed, but this was not mentioned in the main body of the report.

The findings of this study, regarding the efficacy of combination treatment, are difficult to interpret in the absence of a control arm. The potential for selection-bias cannot be excluded given the lack of detail on patients who tested positive for COVID-19, were not included in the study, and were not described among the exclusions. The absence of any detail on safety outcomes is a major study limitation (21).

Molina et al. 28th March 2020 (Case series)

A prospective study of 11 consecutive patients admitted to a French Hospital (APHP-Saint Louis Hospital) who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5) were followed up for virological and clinical outcomes (20). The mean age was 58.7 years and eight patients had significant comorbidities associated with poor outcomes. At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within five days, one patient died, two were transferred to the ICU, and treatment with hydroxychloroquine and azithromycin was discontinued after four days because of QT prolongation in one patient (20). Repeated nasopharyngeal swabs were still positive for SARS-CoV2 RNA in 8/10 surviving patients at days 5 to 6 after treatment initiation (20). As described above for the Gautret et al study, the Molina et al study is limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hyd/az combination therapy, single-agent hydroxychloroquine or azithromycin therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course.

Gautret et al. 27th March 2020 (Case series, Preprint)

A second report by Gautret et al, expanded the initial case series of six patients treated with hydroxychloroquine-azithromycin to 80 patients (19). Patients with confirmed COVID-19 were admitted to the University Hospital Institute Méditerranée Infection in Marseille, France. Patients with no contraindications were offered combination therapy with hydroxychloroquine sulphate 200mg three times daily for ten days plus azithromycin 500mg on day 1 followed by 250mg per day for the next four days. Ceftriaxone (a broad spectrum antibiotic) was added in patients with pneumonia and NEWS score≥5. ECGs were performed on each patient before treatment and two days after treatment began. Hydroxychloroquine-azithromycin treatment was either not started or discontinued after two days on the basis of QTc risk-benefit assessment, and other abnormalities on ECG. Eighty patients who received combination hydroxychloroquine-azithromycin treatment for at least three days and who were followed-up for at least six days were included in the analysis. The median age of patients was 52.5 years; 52.5% were male; 57.5% had at least one chronic condition known to be a risk factor for severe COVID-19. The mean duration between the onset of symptoms and hospitalisation was five days (range 1-17 days). 53.8% and 41.2% of patients presented with LRTI with URTI respectively. Four patients were asymptomatic. 92% of patients had a low NEWS score (0-4), suggesting a mild disease. 53.8% of patients had LDCT compatible with pneumonia within 72 hours of admission. The mean PCR Ct value was 23.4. The mean time between the onset of symptoms and the initiation of treatment was 4.9 days. Treatment was stopped on day 4 in one patient because of the risk of a potential drug interaction. Viral load tested by qPCR was negative in 83% of patients on day 7 and 93% at day 8. Most patients (65/80, 81.3%) were discharged from the authors' unit with a favourable outcome at the time of writing. The mean time from treatment initiation to discharge was 4.1 days (SD 2.2). Three patients were transferred to the ICU, including two deaths. [One death was reported in the original study report. This was subsequently updated to two deaths in report of a separate study by the same investigators] (21). Adverse events were described as rare and minor, occurring on seven occasions (unclear if these are seven events, or seven patients) including nausea/vomiting, diarrhoea and blurred vision.

This study is limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hydroxychloroquine-azithromycin combination therapy, single-agent hydroxychloroquine or azithromycin therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course. The study does not provide information on the status of all patients who were initiated on hydroxychloroquine-azithromycin treatment, only those who received at least three days of treatment or who were followed up for at least six days. It is possible that those patients who discontinued treatment early may have had more severe disease, necessitating a change in treatment.

Evidence for the clinical efficacy of lopinavir-ritonavir for COVID-19

Lopinavir-ritonavir is an antiretroviral fixed drug combination (HIV protease inhibitors), currently licensed in Ireland for the treatment of human immunodeficiency virus (HIV-1). (58) Lopinavir-ritonavir has been shown to have in vitro activity against SARS-CoV-1. (59-61). Limited clinical data has also been reported for lopinavir-ritonavir, combined with ribavirin and interferon alfa, in MERS (62). Lopinavir-ritonavir in combination with interferon-beta 1b is currently under investigation for the treatment of MERS-CoV (63). The potential for benefit from lopinavir-ritonavir treatment in COVID-19 has been well documented (64).

Clinical studies of lopinavir-ritonavir

To date, while observational cohort studies have reported the use of lopinavir-ritonavir (65, 66), the clinical evidence for comparative efficacy is limited to three open-label randomised, controlled studies (two of which failed to demonstrate a benefit for lopinavir–ritonavir versus SoC, and one which did not include a SoC control arm) and observational case reports (27-30)

Randomised controlled trials

Hung et al. 08th May 2020 (Peer-reviewed RCT report)

In a prospective, open-label, randomised, phase II trial in hospitalised adults with COVID-19 across six hospitals in Hong Kong, 127 patients were randomised (2:1) to 14 days treatment with either a combination regimen (n=86) of lopinavir 400 mg and ritonavir 100 mg every 12 hours, ribavirin 400 mg every 12 hours, and interferon beta-1b (if within 7 days of symptom onset, at a dose of 8 million IU on alternate days, up to a maximum of three doses) or to a control regimen (n=41) of lopinavir 400 mg and ritonavir 100 mg every 12 h. Interferon was omitted from the combination regimen in patients recruited after day 7 to avoid its proinflammatory effects. The primary endpoint was the time to negative nasopharyngeal RT-PCR SARS-CoV-2 swab. Eligible patients had to be within 14 days of symptom onset, and the intervention treatment had to be started within 48 h after hospital admission. The primary endpoint was assessed in the intention-to-treat population of all randomised patients. The median age was 52 years, 54% were male, 40% had underlying diseases. The median time to hospital admission from symptom onset was 5 days (IQR 3-7). In the combination group, 52/86 were admitted to hospital 7 days or more after symptom-onset and received double-combination therapy with lopinavir-ritonavir and ribavirin only. Baseline demographics were similar between treatment groups. Disease severity was mild at baseline (NEWS2=2). The combination group had a significantly shorter median time from

start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]), (HR 4.37, 95% CI 1.86 to 10.24: p=0.0010). This finding was driven by the subgroup of patients (approximately 60%) who were treated within 7 days of symptom-onset with triple-combination therapy, as no significant differences in outcomes were observed in the subgroup of patients treated 7 days or more after symptoms onset (with lopinavir-ritonavir and ribavirin only). Secondary endpoints such as time to complete alleviation of symptoms (defined as a NEWS2 of 0), and duration of hospital stay were significantly shorter in the combination group compared with the control group. Six (5%) patients were admitted to the intensive care unit, of whom five required non-invasive ventilator support and one required intubation and ventilator support. No patients died during the study. Adverse events included self-limited nausea and diarrhoea with no difference between the two groups. One patient in the control group discontinued lopinavir–ritonavir because of impaired hepatic enzymes.

This study is limited by its open-label design, though the potential performance- and detection-bias associated with unblinded studies is mitigated somewhat by the use of an objective primary endpoint, and the ITT analysis. The absence of a control arm comprising patients who were treated with SoC is a further limitation as the efficacy of lopinavir-ritonavir, alone or in combination, has not been proven. Evidence suggests that benefit is limited to treatment with the triple-combination regimen when received within 7 days of symptom onset. However, it is difficult to discern between the benefits of early combination treatment and the inclusion of interferon-beta in the combination regimen, as outcomes in the combination regimen are confounded by the omission of interferon beta in 40% of patients who received treatment after 7 days of symptom onset. Results cannot be extrapolated to critically-ill patients.

Li et al 15th April 2020 version 2 (version 1 of this study was published on March 23rd 2020) (RCT report, Preprint)

Li et al initially reported results of the ELACOI (The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection) study (ClinicalTrials.gov Identifier: NCT04252885) on March 23rd 2020 (including 44 patients) and subsequently published version 2 of the report with updated results on 15th April 2020 (including 86 patients) (67). Eighty-six patients with mild/moderate COVID-19 were randomised 2:2:1 to lopinavir 400mg–ritonavir 100mg twice a day monotherapy for 7-14 days (n=34), Arbidol® (umifenovir) 200mg three times daily for 7-14 days (n=35), or no antiviral treatment (n=17). Umifenovir is a haemagglutinin inhibitor antiviral used in China and Russia, with reported efficacy against influenza viruses (68). The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff. The primary outcome was the time of positive-to-negative conversion of SARS-CoV-2 nucleic acid from initiating treatment to day 21, with the enrolment day as the first day of treatment. The cohort included 40 men and 46 women,

with a mean age of 49.4 years. There were some differences between the study populations in mean age, and proportion with underlying chronic diseases (20.6%, 14.3% and 35.3% in the lopinavir-ritonavir, arbidol and control groups respectively). The time from onset to treatment ranged from 3.5 to 6 days across the treatment groups. The mean time to positive-to-negative conversion of SARS-CoV-2 nucleic acid during the 21-day follow-up period was not significantly different between the treatment groups: 9.0 (SD 5.0) in the lopinavir-ritonavir group, 9.1 (SD 4.4) in the arbidol group and 9.3 (SD 5.2) in the control group (P =0.981). No difference was observed between groups in other secondary outcomes including the rate of antipyresis, rate of cough resolution, and rate of improvement on chest CT imaging at day 7 and 14. During the follow-up period, 12 (35.3%) patients in the lopinavir-ritonavir group experienced adverse events, compared with 5 (14.3%) in the arbidol group and none in the control group. More patients treated with lopinavir-ritonavir progressed from mild/moderate to severe/critical status than other two groups.

The study was limited by the small sample size, the lack of blinding of recruiting clinicians and research staff, the restriction to mild/moderate disease and the low level of underlying chronic diseases (67).

Cao et al. 18th March 2020 (Peer-reviewed RCT report)

Cao et al reported results of a randomised, controlled, open-label trial involving hospitalised adult patients with confirmed SARS-CoV-2 infection with an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg. 199 patients were randomised 1:1 to either lopinavir 400mg–ritonavir 100mg twice a day for 14 days, in addition to standard care, or standard care alone (27). The primary end point was the time to clinical improvement defined as the time from randomisation to either an improvement of two points on a seven-category ordinal scale (previously used for an influenza clinical trial conducted by the authors and recommended by the WHO) or discharge from the hospital. The median age of the total cohort was 58.0 years and 60.3% were male. The median time between illness onset and randomisation was 13 days in the treatment group. There were no meaningful between-group differences in baseline characteristics. No difference in the time to clinical improvement was observed between lopinavir–ritonavir and standard care (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality was also similar between the treatment groups (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). A post-hoc analysis revealed a greater numerical difference in mortality between treatment groups, in favour of lopinavir–ritonavir, among patients treated within 12 days after the symptom-onset than among those treated later. Numerical differences in favour of lopinavir–ritonavir were observed in a number of secondary outcomes, including a shorter stay in the intensive care unit (6 days vs. 11 days; difference, −5 days; 95% CI, −9 to 0), but these were not significant. lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

Gastrointestinal adverse events in particular were more common in lopinavir–ritonavir group than in the standard-care group.

The open-label design of this trial is a limitation as it may lead to performance-bias and detection-bias for subjective outcomes. The applicability of this trial to all patients with COVID-19 is uncertain, particularly as the overall mortality (22.1%) in the trial was higher than was been observed elsewhere(69) .

Observational studies

Kim et al. 18th May 2020 (Retracted 14th June, retrospective cohort study, Preprint)

**This study was a retrospective cohort study in a hospital in Korea comparing responses in a subgroup of 97 patients with moderate COVID-19 to various treatments, including hydroxychloroquine, lopinavir-ritonavir, or conservative treatment (52). The authors have withdrawn this manuscript because of the controversy about hydroxychloroquine and potential changes in results after peer-review. The authors intend to share their results in formal publication and do not wish this work to be cited as reference for the project (57). **

Case reports

Han et al 19th February 2020 (Case report)

One case report of a 47-year old man treated with lopinavir-ritonavir in Wuhu, China, describes the use of lopinavir-ritonavir 800/200 mg daily *(ERG note: this is higher than the licensed dose for this treatment, and higher than is recommended in international COVID-19 treatment guidelines)* dose than the following hospital transfer due to acute exacerbation of clinical symptoms including expiratory dyspnoea, poor diet, and lethargy reported quick improvement of the clinical symptoms (28). The exact timing of treatment was not reported but it is assumed to be at least nine days post symptom-onset, given the reported date of hospital transfer. Treatment also included methylprednisolone, recombinant human interferon alfa-2b, ambroxol hydrochloride and moxifloxacin hydrochloride (28).

Lim et al 13th February 2020 (Case report)

Another case report of a 54-year old man in Korea, described the use of lopinavir-ritonavir 400mg-100mg twice daily from day ten of illness (29). No serious respiratory symptoms were reported. β-coronavirus viral load started to decrease on the day after treatment initiation and no detectable or little coronavirus titres were observed from day 17 of illness. Other treatments over the course of the patient follow-up included ceftriaxone, tazobactam, levofloxacin, azithromycin, and peramivir. The authors acknowledged that that the decreased load of SARS-CoV-2 could have resulted from the natural course of the

healing process rather than administration of lopinavir/ritonavir, or both (29). Subsequent commentary has suggested that the pattern of viral titres suggests that the natural course of the disease may be a more likely driver of improvement in this case (51).

Evidence for the clinical efficacy of remdesivir for COVID-19

Remdesivir is a broad-spectrum antiviral drug. It is the first medicine against COVID-19 to be recommended for authorisation in the EU. Remdesivir was recommended for a conditional marketing authorisation on 25th June 2020, to fulfil an unmet medical need with less complete data than normally expected. The company must submit final reports of the remdesivir studies to the European Medicines Agency (EMA) by December 2020 as well as final data on mortality by August 2020. Data on remdesivir were assessed through a rolling review procedure, which assessed clinical and non-clinical data, as well as supporting safety data from compassionate use programmes. The recommended therapeutic indication of remdesivir is for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. The recommended dose is a single loading dose of 200mg given by IV infusion on Day 1, followed by 100mg given once daily by IV infusion from Day 2 onwards for a total duration of treatment of 5-10 days. Remdesivir was first used as an investigational agent having shown effective inhibition of SARS-CoV-2 in vitro, and in vivo in a rhesus macaque model (42, 70). Efficacy was previously shown in MERS and SARS-CoV-1 animal models (71, 72). An extensive clinical safety database exists from its investigational use in Phase I, II and II trials for the Ebola virus and MEURI (39). Numerous clinical trials of remdesivir are ongoing, and three RCTs have published results (32-34).

Clinical Studies of remdesivir

The first RCT to publish results on the efficacy of remdesivir reported disappointing results (34). This was followed, however, by three press-releases reporting positive results from three additional studies, from the NIH and Gilead Sciences (the developers of remdesivir), two of which have since been published as full reports (32-34, 73, 74) (36). One of these studies, the ACTT-1 Study, was the main study considered in the EMA assessment. Case reports and a case series, describing the use of remdesivir, in the United States have also been published (37, 75, 76).

Randomised controlled trials

Goldman et al. May 27th 2020 (Peer-reviewed RCT)

An open-label RCT analysed data from 397 patients hospitalised with severe COVID-19 (oxygen saturation of 94% or less while breathing ambient air, and radiologic evidence of

pneumonia). Patients were randomised 1:1 to remdesivir for either 5 days or 10 days, at a dose of 200mg on day 1 and 100mg once daily thereafter. A control group (placebo, standard of care, or other control) was not included. The primary end point was clinical status on day 14, assessed on a 7-point ordinal scale consisting of severity categories ranging from 1=death to 7=not hospitalised. Baseline demographic characteristics were similar between groups however baseline disease severity was significantly worse in the 10-day group than the 5-day group, with more patients requiring high-flow oxygen support (30% vs 24%, p=0.02). The median age of the cohort was 61-62 years, and 60-68% were male. Hypertension and diabetes were present in 23% and 50% of the cohort, respectively. A complete course of treatment was received by 86% of patients in the 5-day group and 44% of patients in the 10-day group, though the median duration was 9 days (IQA 5-10). A clinical improvement of 2 points or more on the ordinal scale occurred in 65% of patients in the 5-day group and in 54% of patients in the 10-day group. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P=0.14). Time to clinical improvement was also similar between groups 10 days vs 11 days. More patients in the 10-day treatment group experience adverse events compared with the 5-day group (35% vs 21%), possible due to the longer exposure to treatment and/or the more severe disease status in the 10-day group. The most common adverse events were nausea (9% of patients), acute respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).

The clinical relevance of the study findings are limited at this stage due to the lack of a control arm, and a limited existing evidence base supporting the efficacy of remdesivir compared with placebo or standard of care. The results of the study are limited to patients with severe disease, and cannot be extrapolated to critical disease as few patients were receiving mechanical ventilation at the time of treatment initiation. The open-label design of the study is a potential source of bias, particularly with regard to outcome assessment.

Beigel et al. (ACTT-1) May 22nd 2020 (Peer-reviewed RCT)

A preliminary report from a double-blind RCT of remdesivir in COVID-19 (ACTT-1) was published on May 22nd 2020, following an initial press release of interim results from the NIH on April 29th 2020 (32, 73). The ACTT trial (Adaptive COVID-19 Treatment Trial), is an adaptive, randomised, double-blind, placebo-controlled trial, designed to evaluate the safety and efficacy of investigational therapeutics in hospitalised adults diagnosed with COVID-19 (NCT04280705) (73, 77). The study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID, part of NIH). ACTT is a multicentre trial, conducted in up to approximately 100 sites globally, predominantly in the US but also Europe, Singapore, Mexico, Japan and Korea. ACTT-1 investigated the efficacy of remdesivir compared with placebo in adults hospitalized with COVID-19 with evidence of lower respiratory tract

involvement. Between February 21st and April 19th 2020, 1,063 patients were randomised 1:1 to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. All patients received supportive care according to the SoC for the trial site hospital. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalisation for infection control purposes only. Secondary outcomes included mortality at 14 and 28 days after enrolment and safety outcomes. Results were reported following a planned interim analysis at which time the data and safety monitoring board recommended that preliminary results be provided to the NIAID. The NIAID subsequently decided to make the results public and treating physicians could request to be made aware of the treatment assignment of patients who had not completed day 29, if clinically indicated. A large proportion of patients in each treatment group, 24.5% in the remdesivir group and 32.4% in the placebo group, had not completed the day 29 follow-up visit. The mean age of patients was 58.9 years and 64.3% were male. The majority of patients were enrolled in North America (79.8%) or Europe (15.3%). Most patients had two or more (52.1%) of the prespecified coexisting conditions at enrolment, most commonly hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%). The median time between symptom onset and randomisation was 9 days. Most patients (88.7%) had severe disease at enrolment. Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days vs 15 days; rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). Benefit was most pronounced for patients with an ordinal score of 5 at baseline (i.e. requiring supplemental oxygen) (rate ratio for recovery 1.47, 95% CI, 1.17 to 1.84). This is likely due to the large sample size in this category, as the interaction test of treatment by baseline ordinal score was not significant. Confidence intervals were wide (and spanned zero) for other baseline ordinal scores. Results were similar between patients randomised during the first 10 days and more than 10 days after the onset of symptoms. Mortality was numerically lower in the remdesivir group than in the placebo group by day 14, but the difference was not significant (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04; 1,059 patients). As described, a large number of patients have yet to complete the study. Serious adverse events occurred in 21.1% and 27.0% of patients in the remdesivir and placebo groups, respectively (32).

The interpretation of mortality data from this study is limited by the large number of patients yet to complete the study. Even with complete follow-up, the ability of the trial to demonstrate a mortality benefit from treatment is hampered by the early unblinding of treatment assignment and the facility to discontinue placebo. Of some concern is a change in the primary outcome mid-trial, as observed from a comparison of study record changes on Clinicaltrials.gov (77). The trial was initially designed (and began recruiting) to investigate the difference in clinical status between patients treated with remdesivir compare with placebo, defined by an 8-point ordinal scale, including various combinations of death, hospitalisation, degree of ventilation/oxygenation and limitation of activities (Day 15). The primary endpoint was changed during the study and the initial primary endpoint changed to

a secondary endpoint. This change was made before any data were revealed to investigators, when only 72 patients were enrolled (78). The change was made in response to emerging information, external to the trial, indicating that COVID-19 may have a more protracted course than previously appreciated leading to concern that a difference in outcome after day 15 would have been missed by a single assessment at day 15 (32).

Wang et al. 29th April 2020 (Peer-reviewed RCT report)

In an investigator-initiated, randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China, 237 patients were assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 to 10 in single daily infusions) or the same volume of placebo infusions for 10 days (34). Patients were seriously ill with RT-PCR-confirmed SARS-CoV-2 infection, pneumonia confirmed by chest imaging, $Sp0_2$ ≤94% on room air or a PaO_2/FiO_2 ratio of ≤300mgHg, and were within 12 days of symptom onset. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary clinical endpoint was time to clinical improvement within 28 days after randomisation, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first (34). The study did not reach its target enrolment (n=453) because of marked reductions in new presentations, and presentation of patients at a later course of disease due to limited availability of hospital beds. The median age of the cohort was 65 years, 56% were male. Most patients (82%) required supplemental oxygen but not high-flow or mechanical ventilation. Co-morbidities were present in 71% of patients, with slightly more patients in the remdesivir group having hypertension, diabetes and coronary artery disease than the placebo group. A higher proportion of remdesivir recipients had a respiratory rate of more than 24 breaths per minute (23% vs 14%).The time from symptom onset to starting study treatment was 11 days. More patients in the placebo group had been symptomatic for 10 days, compared with the remdesivir group. The time to clinical improvement in the remdesivir group was not significantly different to that of the placebo group (median 21.0 days vs 23.0 days, HR 1.23, 95% CI 0.87 to 1.75). The authors reported a numerical improvement in time to clinical improvement in the subgroup of patients receiving remdesivir within 10 days of symptom onset, though this was not statistically significant, and the study was not powered to detect a difference in this subgroup. No difference was observed in 28-day mortality between the two groups (14% in the remdesivir group vs 13% in the placebo group; difference). No significant differences were observed between the two groups in other secondary endpoints including duration of invasive mechanical ventilation or oxygen support, hospital length of stay or time to discharge. Adverse events occurred at a similar frequency in both groups, though more patients in the remdesivir group than the placebo group discontinued the study drug because of adverse events or serious adverse events (12% vs 5%).

The study is limited by its failure to enrol an adequate sample size, resulting in an underpowered trial which may not be capable of demonstrating an effect, if one exists. As such, the findings of the study are inconclusive, showing no compelling benefit of treatment, but also unable to rule out the possibility of benefit. The patient population had less severe disease than other published cases treated with remdesivir (37). The duration of symptoms prior to starting treatment was longer than is expected in other ongoing clinical trials of remdesivir e.g. ACTT trial requires a positive SARS-CoV-2 confirmation <72 hours prior to randomisation. Though no important differences were apparent between groups in the use of lopinavir-ritonavir (28%) and corticosteroids (66%), the potential for concomitant therapy to impact on efficacy cannot be outruled (34).

Press Release

Gilead Sciences. 01st June 2020 (Press-release of initial study results)

Top line results were announced from the Phase III SIMPLE trial in hospitalized patients with moderate COVID-19 pneumonia (36). Hospitalised patients, with SpO2>94% on room air, were randomised 1:1:1 to open-label remdesivir for 5 days (n=191) or 10 days (n=193) or standard of care alone (n=200). The primary outcome was the odds ratio for improvement on a 7-point ordinal scale (ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death) on day 11. At day 11, an improvement of ≥2 points in the ordinal scale was observed in 70%, 65% and 61% of patients treated with 5-day remdesivir, 10-day remdesivir and standard of care, respectively. Results were reported as significant for 5-day remdesivir, and favourable, trending toward but not reaching statistical significance for 10-day remdesivir. No new safety signals for remdesivir were reported. Publication of full study reports is awaited.

Case series

Grein et al. 10th April 2020 (Peer-reviewed case series)

A case series of 53 hospitalised patients with severe COVID-19 who received at least one dose of remdesivir on a compassionate-use basis between January 25th and March 7th 2020, was published by Gilead Sciences, the developers of the investigational drug (37). The cases were drawn from the United States, Europe, Canada and Japan. Patients received a 10-day course of remdesivir, at a dose of 200 mg IV on day 1, followed by 100 mg daily up to day 10. The cohort had a median age of 64 years, and 40 (75%) were male. At baseline, the majority of patients (34 [64%]) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving extracorporeal membrane oxygenation (ECMO). The median duration of symptoms before treatment initiation was 12

days, and the median duration of invasive mechanical ventilation before treatment initiation was 2 days (IQR 1-8). Forty patients (75%) received the full 10-day course of remdesivir, 10 (19%) received 5 to 9 days of treatment, and 3 (6%) received less than 5 days of treatment. During a median follow-up of 18 days, seven patients (13%) died. Mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation. Thirty-six patients (68%) had an improvement in the category of oxygen-support, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged by the date of the most recent follow-up. Thirty-two patients (60%) reported adverse events during follow-up, most commonly including increased hepatic enzymes, diarrhoea, rash, renal impairment, and hypotension. Twelve patients (23%) had serious adverse events. Viral load data were not collected during this compassionate-use program. The case series excluded eight patients for whom post-baseline data were missing.

Interpretation of the results of this study is limited by the lack of a control group, the short duration of follow-up and the high degree of missing data.

Clinical trials of investigational treatments for COVID-19

Researchers have registered hundreds of clinical trials for COVID-19, many of which are actively recruiting (79-81). COVID-19 trials need to be well designed and adequately powered to generate robust evidence (82). A number of large, international clinical trials of investigational treatments for COVID-19 are underway in Europe. These include the SOLIDARITY trial, the REMAP-CAP trial, the Discovery trial and the RECOVERY trial. These trials are all adaptive in design, whereby aspects of the study protocol, including interventions, may be changed on the basis of interim analysis and emerging evidence. Notable adaptations since the initiation of these trials have included the stopping of recruitment into the hydroxychloroquine arm of some of the trials due to no evidence of benefit. Following consideration of trial results, the UK's medicines regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), also instructed UK clinical trialists using hydroxychloroquine for COVID-19 to suspend recruitment of further participants.

REMAP-CAP

The Randomised Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) Study is an international trial designed to evaluate the effect of a range of interventions to improve outcomes of patients admitted to intensive care with community-acquired pneumonia (ClinicalTrials.gov Identifier: NCT02735707) (83). REMAP-CAP is enrolling patients with COVID-19 in North America, Europe, Australia and New Zealand, and expanding rapidly. In January 2020, REMAP-CAP was already enrolling patients in 52 ICUs in 13 countries, and in February 2020 the trial transitioned in to pandemic model with several design adaptations for COVID-19 disease (83). To date, 90 study locations across Europe, Australia, New Zealand and North America are participating in the study, including three Irish hospitals: Beaumont Hospital, St. Vincent's University Hospital and University Hospital Galway (84). The aim is to generate evidence that can be applied during the COVID-19 pandemic to reduce mortality, reduce intensive care use, and reduce morbidity in severely ill patients with COVID-19 infection. The core trial randomises patients to multiple interventions within four treatment domains representing 240 treatment regimens: antibiotics (ceftriaxone plus macrolide, piperacillin-tazocin plus macrolide, amoxycillin-clavulanate plus macrolide, respiratory quinolone); antiviral therapy for influenza (no antiviral agent, oseltamivir (5 days or 10-days)); host immunomodulation with extended macrolide therapy (3-5 days or 14 days); and alternative corticosteroid regimens (no corticosteroid, shock-dependent hydrocortisone, 7-day hydrocortisone). Additional domains were implemented for COVID-19. Antiviral therapy was amended to include hydroxychloroquine and lopinavir-ritonavir; Immunomodulation was amended to include interferon-beta 1a, anakinra (interleukin-1 receptor antagonist), and interleukin-6 receptor antagonists; the corticosteroid domain was modified to include a higher dose. Other domains are under construction. The trial generates estimates of superiority, inferiority and

equivalence between regimens on the primary outcome of 90-day mortality, stratified by presence or absence of concomitant shock and proven or suspected influenza infection. The trial will also compare ventilatory and oxygenation strategies and has capacity to address additional questions rapidly during pandemic respiratory infections. REMAP-CAP begins with randomisation balanced across interventions. Thereafter, a Bayesian inference model is re-estimated at regular intervals with updated trial data, generating updated randomization weights for on-going random assignments. Interventions that are faring well will be randomly assigned more commonly and those faring less well will be assigned less commonly. New interventions and domains are introduced via protocol modifications (83, 84).

World Health Organisation Solidarity

The Solidarity trial is an international, multi-centre, adaptive, randomised, open-label, controlled clinical trial launched by the World Health Organization (WHO) and partners (EU 2020-001366-11, EU2020-000982-18, NCT04330690, NCT04321616) (55, 85-88). The trial will evaluate the clinical efficacy and safety of four treatment options against standard of care for COVID-19. The treatment options in the trial are remdesivir; lopinavir-ritonavir; lopinavir-ritonavir with interferon beta-1a; and chloroquine or hydroxychloroquine. As of May 25th 2020, over 400 hospitals in 35 countries are actively recruiting patients and nearly 3500 patients have been enrolled from 17 countries. Patients include adults, hospitalised with COVID-19. The Solidarity study is intended to allow for multiple adaptations, including the primary endpoint and intervention arm which may be adapted based on emerging data on performance characteristics, and efficacy, respectively (55). Individual country protocols have been published for the Solidarity trial including Norway, Spain and Canada, which vary in reported primary outcomes e.g. all-cause mortality, clinical status on a10-point ordinal scale. Main secondary endpoints include duration of hospital stay and time to first receiving ventilation or intensive care (85-88). On 24/5/20, following publication of an observational study on hydroxycholoroquine and chloroquine in COVID-19 by Mehra et al, discussed earlier in this RER, the Executive Group of the Solidarity Trial, representing 10 of the participating countries, implemented a temporary pause of the hydroxychloroquine arm while the safety data was reviewed by the Data Safety Monitoring Board. Findings of this review, announced 03/06/20, found no cogent reasons to recommend modifications to the trial protocols. However, a subsequent review of data from the SOLIDARITY trial showed that hydroxychloroquine does not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with standard of care. The hydroxychloroquine arm of the SOLIDARITY trial was stopped on 17/06/20(55). On 26th June a press release announced Irelands participation in the trial.

Discovery

The Discovery trial was launched by Inserm, a public scientific and technological institute which operates under the joint authority of the French Ministries of Health and Research (EU 2020-000936-23) (89). Discovery is a multi-centre, adaptive, randomised trial of the safety and efficacy of treatments of COVID-19 in hospitalised adults. The study will analyse the safety and efficacy of four investigational therapies in 3,200 participants hospitalised with COVID-19 across France, Belgium, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK. The investigational therapies include remdesivir, lopinavir and ritonavir in combination, the latter being administered with or without interferon beta and hydroxychloroquine (90). The primary endpoint is subject clinical status (on a 7-point ordinal scale) at day 15 (89). In line with the SOLIDARITY trial investigators, enrolment into the hydroxychloroquine group of the Discovery trial was suspended on 24th May 2020, following the publication of observational studies (91).

UK trials

Key national priority trials in the UK include the PRINCIPLE trial, for higher risk patients in primary care (www.principletrial.org) the RECOVERY trial, for hospitalised patients (www.recoverytrial.net) and REMAP-CAP, for critically ill patients (54, 83, 84, 92). The RECOVERY trial is coordinated by the Nuffield Department of Population Health, Oxford, and is aligned with the WHO Solidarity trial protocol, using the same drug doses. Like the other international trials, RECOVERY has an adaptive design, starting with the Investigational agents lopinavir-ritonavir, low-dose dexamethasone, hydroxychloroquine and azithromycin (54). Data is reviewed by the independent DMC about every two weeks to determine if there is evidence that would be strong enough to affect national and global treatment of COVID-19. On May 23rd, chief investigators initially announced that it was safe to continue the trial, following a review of unblinded data, which was conducted in response to concerns in relation to hydroxychloroquine (6, 8, 11). On June 4th, the DMC recommended the chief investigators review the unblinded data on the hydroxychloroquine arm of the study. Preliminary results of the review concluded that there is no beneficial effect of hydroxychloroquine in patients hospitalised with COVID-19. These results are discussed in more detail in the *Evidence for Clinical Efficacy* section of this document. Enrolment into to the hydroxychloroquine arm of the trial has been stopped (2).

United States: ACTT and Orchid trials

Three studies have been launched by the National Institute of Health in the United States. The Outcomes Related to COVID-19 treated with hydroxychloroquine among In-patients with symptomatic Disease study, or ORCHID Study, is being conducted by the National Heart, Lung, and Blood Institute (NHLBI). The National Institute of Allergy and Infectious

Diseases (NIAID) is supporting the Adaptive COVID-19 Treatment Trial (ACTT). The AIDS Clinical Trials Group (ACTG) (NIAID-funded is conducting the A5395 study. ORCHID is a multicentre, double-blind, placebo-controlled, randomised clinical trial evaluating hydroxychloroquine for the treatment of adults hospitalised with COVID-19 (NCT04332991) (93). The primary outcome is based on the COVID Ordinal Outcomes Scale on Day 15. The ORCHID study was stopped after its fourth interim analysis by the DSMB which determined that while there was no harm, the study drug was very unlikely to be beneficial to hospitalised patients with COVID-19. More than 470 were enrolled at the time of study's closure. A full report of study results is awaited. The ACTT trial is an adaptive, randomised, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalised adults diagnosed with COVID-19 (NCT04280705) (77). The study is a multicentre trial that will be conducted in up to approximately 100 sites globally, predominantly in the US but also Europe, Singapore, Mexico, Japan and Korea. The adaptive nature of the trial allows an independent data and safety monitoring board to actively monitor interim data to make recommendations about early study closure or changes to study arms (77). Interim results from the ACTT trial, reported on April 29th, showed some benefit from remdesivir compared with placebo. Interim results are described in the remdesivir section of this review, and a full study report is awaited (73). The next iteration of the ACTT trial, ACTT2, will examine if adding baricitinib, a JAK inhibitor licensed for the treatment of rheumatoid arthritis, will provide additional benefit when added to remdesivir The ACTT2 trial does not include a placebo arm (94). The A5395 study will evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalisation or death in symptomatic adult outpatients with COVID-19. Participants will receive study treatment for 7 days and will be followed for an additional 23 weeks (95).

Other investigational antivirals

A number of other drugs are being developed/repurposed as potential therapeutic candidates for COVID-19. The following section is a descriptive summary of new and emerging data which has not been subjected to a rapid critical appraisal. This list is not exhaustive and will be updated periodically by the ERG.

Favipravir

An open-label study by Cai et al comparing favipravir to lopinavir-ritonavir, previously included in Version 1 of this Rapid Evidence Review, was withdrawn from the publisher's website at the request of the author(s) and/or the editor (96). The study has therefore been removed from this review.

Favipravir is an RNA-dependent RNA polymerase (RdRp) inhibitor approved for the treatment of influenza in China and Japan, and previously identified by the WHO as a promising candidate for testing in patients with Ebola virus disease (97, 98). In an in vitro study, inhibition of SARS-CoV-2 infection in Vero E6 cells was not as effective with favipravir as it was for remdesivir or chloroquine (42). Chen et al reported on a prospective, multicentre, open-labelled, randomised study assessing the clinical efficacy and safety of favipravir versus arbidol as treatment for COVID-19 (99). Two hundred and thirty six patients aged ≥18 years with COVID-19 pneumonia, within 12 days of initial symptoms were randomised 1:1 (116:120) to routine treatment plus favipravir (1600mg twice daily on day one, 600mg twice daily from day two onwards), or routine treatment plus arbidol 200mg three times daily, for a duration of 7-10 days. Exclusion criteria included severe patients whose expected survival time was expected to be less than 48 hours, among others. The primary outcome was the clinical recovery rate at 7 days or the end of treatment, defined as continuous (>72 hours) recovery of body temperature, respiratory rate, oxygen saturation and cough relief after treatment. Results were stratified for moderate patients with COVID-19, severe patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. The authors did not include subgroup analysis in the statistical plan, and it is therefore unlikely that the study was powered to detect a difference between subgroups. 46.6% of patients were male, 70% of patients were aged ≥65 years, 33% had hypertension and 19% had diabetes. 89% of patients had severe COVID-19, with slightly more patients in the arbidol group having severe COVID-19 compared with the favipravir group (93% vs 89%). No significant difference in basic characteristics was observed between the two groups. There was a notable difference in the proportion of patients receiving other concomitant antivirals, which may have included ribavirin, chloroquine and/or interferon (24.32% in the arbidol group vs 11.22% in the favipravir group, p=0.0045). The clinical recovery rate was 51.67% (62/120) in the arbidol group and 61.21% (71/116) in the favipravir group after a 7 day's antiviral treatment (non-significant difference 9.54%, 95% CI: -3.05% to 2.2%,

P=0.1396). The difference in recovery rate was more pronounced for patients with moderate disease compared to severe disease (15.6% vs 5.6% difference between treatment groups). There was minimal difference in clinical recovery rate between the two treatment groups in patients with hypertension and/or diabetes. For patients with moderate disease, and for patients with hypertension and/or diabetes, the time of fever reduction and cough relief (present in 58% and 59% of all patients with moderate disease, respectively, and in 38% and 62% of all patients with hypertension and/or diabetes, respectively) was reported to be significantly shorter in the favipravir group than in the arbidol group (mean time not reported, $p<0.0001$). No statistically significant differences in auxiliary oxygen therapy or non-invasive mechanical ventilation were observed between the two treatment groups, though numerical differences favoured favipravir. There was an imbalance in the severity of COVID-19 between the treatment groups with the arbidol group having slightly more patients with severe disease. This study was limited by its open-label design, lack of power for subgroup analysis, imbalances in the treatment group in disease severity and in the proportion of patients receiving other concomitant antivirals, with the arbidol group having slightly more patients with severe disease, and also more patients receiving other antivirals. While the stratified analysis based on severity is unaffected by the severity imbalance, the impact of concomitant antiviral therapy on clinical outcomes is unknown. The ERG is not aware that favipravir is readily available for use in Ireland.

Ribavirin

Ribavirin is licensed for the treatment of hepatitis C virus, and is included in Chinese COVID-19 treatment guidelines, preferably in combination with interferon or lopinavir-ritonavir (100). The WHO considered that ribavirin does not appear like a candidate worth further investigating, based on the available evidence. This was based on experience with its evaluation in SARS in Canada in 2003 which may have resulted in higher mortality than in other countries. Toxicity risks, such as reduced haemoglobin concentration, were also considered undesirable in patients with respiratory disorders (39).

Danoprevir

Danoprevir (Ganovo®) (a HCV protease (NS3/4A) inhibitor approved and marketed in China since 2018 for chronic hepatitis C virus), boosted by ritonavir was shown to be safe and well-tolerated in a small non-comparative study (n=11) of “moderate” COVID-19 patients at the Nineth Hospital of Nanchang, China (ClinicalTrials.gov Identifier: NCT04291729) (101). Eligible patients had demonstrated respiratory symptoms and imaging-confirmed pneumonia. After 4 to 12 days’ treatment, all eleven patients enrolled were discharged from hospital (101). The ERG is not aware that danoprevir is readily available for use in Ireland.

Other treatments with possible anti-viral activity

Interferons

Interferon-alpha and –beta are type I interferons, made and released by host cells in response to the presence of several viruses, that help regulate the activity of the immune system. Interferons are included in ongoing COVID-19 clinical trials, primarily as part of combination therapy targeting both virus replication and the host's inflammatory response. Interferon-beta 1a and interferon-beta 1b are licensed in Ireland for the treatment of multiple sclerosis. Interferon-alpha 2b is licensed in Ireland for the treatment of chronic hepatitis B and C and various haematological malignancies. Both interferon-alpha and –beta have shown effective in vitro inhibition of SARS-CoV-1 replication, with interferon-beta showing the greatest potency (102). Clinical improvements have been observed in vivo with interferon-beta in MERS-CoV (103).The MIRACLE study in Saudi Arabia is assessing the combination of interferon-beta 1b with lopinavir-ritonavir for the treatment of MERS-CoV (63). A randomised, double-blind, placebo-controlled trial of interferon-beta-1a 10 mcg once daily for six days for the treatment of ARDS in 301 adults with moderate to severe ARDS, did not show improvement in death or ventilator-free days over 28 days (104). Interferon-alpha is included in Chinese COVID-19 treatment guidelines (5 million units (or equivalent), nebulised inhalation, twice daily) preferably in combination with ribavirin or lopinavir-ritonavir (100). COVID-19 treatment guidelines from the National Institutes of Health (NIH, US) recommend against the use of interferons, except in the context of a clinical trial, due to the absence of benefit when interferons were used in other coronavirus infections (i.e., MERS, SARS), the lack of clinical trial results in COVID-19, and the significant toxicities of interferons outweigh the potential for benefit (25).

Meplazumab

Meplazumab is an anti-CD147 humanised IgG2 monoclonal antibody, which has shown to be effective in vitro inhibition of SARS-CoV-2 replication and virus-induced cytopathic effect in Vero E6 cells (105). An open-label, concurrent controlled trial at Tangdu Hospital of Fourth Military Medical University in Xi'an, China, evaluated whether meplazumab, as add-on therapy, improves patients with COVID-19 pneumonia. Eligible patients were described as having "common, severe or critical COVID-19 pneumonia", and received add-on administered 10 mg meplazumab intravenously at days 1, 2, and 5. The primary study endpoint was the virological clearance (i.e. negative conservation rate and time to negative) using qRT-PCR in nasopharyngeal swabs samples. (ClinicalTrials.gov Identifier: NCT04275245) Patients hospitalised in the same period were observed as concurrent control. The clinicaltrials.gov listing for this trial described it as a single centre, single-arm trial. Seventeen patients were allocated to meplazumab and 11 hospitalised patients who met the inclusion criteria and with no exclusion criteria signs were collected as concurrent

control in the same period. All patients received recommended therapy according to local guidelines, including antivirals. Improvements among the meplazumab group in terms of time to virological clearance, time-to-discharge, time to virological clearance and inflammatory markers were reported (106). No adverse effect was found in meplazumab-treated patients. The ERG is not aware that meplazumab is readily available for use in Ireland.

Darunavir/cobicistat

Darunavir (in combination with lopinavir or cobicistat) has been included in Italian COVID-19 treatment guidelines, in place of lopinavir-ritonavir if it is unavailable (107, 108). Darunavir is a HIV protease inhibitor which is licensed, in combination with a CYP3A inhibitor lopinavir or cobicistat, for the treatment of HIV-1. The in vitro antiviral activity of darunavir against a clinical isolate from a patient infected with SARS-CoV-2 was assessed by a team of researchers from Janssen Pharmaceuticals, the pharmaceutical company which originally developed and commercialised darunavir (109). Darunavir showed no activity against SARS-CoV-2 at clinically relevant concentrations (EC50 >100 μM), while remdesivir, used as a positive control, showed potent antiviral activity (EC50 = 0.38 μM). The authors concluded that the data do not support the use of darunavir for treatment of COVID-19 (109). Janssen also reported that results from a single centre, open label, randomised, and controlled trial conducted at Shanghai Public Health Clinical Center (SPHCC) of darunavir/cobicistat in treating 30 COVID-19 patients showed that darunavir/cobicistat was not effective (110). COVID-19 treatment guidelines from the National Institutes of Health (NIH, US) recommend against the use of HIV protease inhibitors, except in the context of a clinical trial (25).

Appendix 1 – Search Strategy

A targeted literature review was conducted to inform the Rapid Evidence Review based on a search strategy developed by the Information Specialist at the National Centre for Pharmacoeconomics. A typical hierarchy of evidence was considered in the search, from highest to lowest:

- Systematic Literature Reviews and meta-analyses
- Randomised Controlled Trials
- Observational studies
- Published expert opinion

The landscape Review of consensus clinical guidelines and international recommendations from WHO and EMA was also conducted. . Clinical trial registers in the EU, US and China were searched for evidence of ongoing or completed clinical trials.

Search strategy 26th June 2020

Source	Search
Pubmed	2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR ((wuhan AND coronavirus) AND 2019/12[PDAT]:2030[PDAT])
	AND ("Chloroquine"[Mesh]) OR "Hydroxychloroquine"[Mesh]
	AND "Lopinavir"[Mesh] OR "lopinavir-ritonavir drug combination" [Supplementary Concept]
	AND "remdesivir" [Supplementary Concept]
LitCovid	chloroquine or hydroxychloroquine
	lopinavir
	remdesivir
MedRxiv	Preselected COVID-19 SARS-CoV-2 preprints from medRxiv or bioRxiv
Google Scholar:	COVID-19 coronavirus OR "coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” AND
	"chloroquine" OR "hydroxychloroquine"
	"lopinavir" or "lopinavir-ritonavir"
	"remdesivir"
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2)
	AND chloroquine or hydroxychloroquine
	AND lopinavir
	AND remdesivir
clinicaltrialsregister.eu	COVID-19

Appendix 2 –WHO and EMA recommendations

World Health Organisation (WHO)

World Health Organisation Interim Guidance on the Clinical management of COVID-19 (29 May 2020), advises that chloroquine and hydroxychloroquine (+/- azithromycin), antivirals, immunomodulators and plasma therapy, not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials. This guidance is based on existing published literature which does not provide high-quality evidence in favour of any of these agents, and important side-effects have been described (111). Outside of clinical trials, the following criteria should be met for access to investigational therapeutics: 1) no proven effective treatment exists; 2) it is not possible to initiate clinical studies immediately; 3) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis; 4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; 5) adequate resources are available to ensure that risks can be minimized; 6) the patient's informed consent is obtained; and 7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community (112).The WHO R&D blueprint Informal Consultation of prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection (24 Jan 2020) identified remdesivir as the most promising candidate therapeutic based on the broad antiviral spectrum, the in vitro and in-vivo data for coronavirus and the extensive clinical safety database (39).

European Medicines Agency (EMA)

On the basis of preliminary results from the ACTT study, the EMA completed a rolling review of data on the use of remdesivir to treat COVID-19 on 15 May 2020 and is awaiting an application for a conditional marketing authorisation. The EMA has made a number of recommendations relating to hydroxychloroquine and chloroquine, including:

- For COVID-19, chloroquine and hydroxychloroquine should preferably be used in the context of clinical trials. Outside clinical trials, they can be used in national emergency use programmes in hospitalised patients under closer supervision.
- Healthcare professionals should closely monitor patients with COVID-19 who are receiving chloroquine and hydroxychloroquine given the serious side effects that can results from treatment with these treatments.
- Chloroquine and hydroxychloroquine should continue to be used in chronic conditions. In order to prevent unnecessary strain on supply chains, patients should only receive

their usual supply of medicines. Healthcare professionals should not write prescriptions that cover more than the usual duration (35, 113, 114).

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