Rapid Evidence Review

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

Version 15, 27th August 2021

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 between version 14 (05th February) and version 15 (27th August 2021):

New clinical evidence:	
Author, study design *(topic)*	
Ohl et al, *retrospective cohort study (Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19)*	Page 20
Coppock et al, *retrospective cohort study (COVID-19 treatment combinations and associations with mortality in a large multi-site healthcare system)*	Page 21
Garibaldi et al, *retrospective cohort study (Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19)*	Page 21
Garcia-Vidal et al, *retrospective cohort study (Real-life use of remdesivir in hospitalized patients with COVID-19)*	Page 22
Medta et al, *retrospective cohort study (A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis)*	Page 23
Flisiak et al, *retrospective cohort study (Remdesivir-based therapy improved recovery of patients with COVID-19 in the SARSTer multicentre, real-world study)*	Page 24
Arabi et al, *RCT (Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial)*	Page 32, 61
Réa-Neto et al, *RCT (An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients)*	Page 33
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Consensus guideline updates:	
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SSC *(remdesivir, hydroxychloroquine, lopinavir-ritonavir)*	Table 1
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NICE (Remdesivir)	Table 1

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

Clinical evidence for the use of antivirals in the treatment of COVID-19 is reviewed on an ongoing basis by the COVID-19 Evidence Review Group. On the basis of preliminary antiviral prioritisation recommendations by the World Health Organisation, the review focuses on remdesivir, hydroxychloroquine and lopinavir-ritonavir. A landscape analysis of consensus clinical guidelines and international recommendations from WHO and EMA is also provided. Emerging evidence on other antiviral therapeutic candidate antivirals is also monitored and summarised.

Many large randomised controlled trials have now been published and provided and some have provided robust evidence. To date 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. A number of high-quality, methodologically robust clinical trials, in large numbers of patients have concluded, and provide credible evidence on the efficacy and safety of investigational antiviral agents for COVID-19; others are ongoing or have provided inconclusive evidence. Some of the studies included in this review are described in press-releases or 'preprints' i.e. unpublished, non-peer-reviewed scientific manuscripts[1].

A number of living systematic reviews and network meta-analyses comparing treatments for COVID-19 have been published and are updated regularly as new evidence becomes available (1-4).

Key points on remdesivir: *RCTs have not demonstrated convincing evidence that remdesivir is effective in reducing mortality in COVID-19. Evidence of benefit with remdesivir in recovery-time in patients on supplemental oxygen at baseline is inconsistent. Further evidence from large RCTs are necessary to address uncertainties. The optimal duration of treatment is also uncertain. Studies have shown no incremental benefit of 10 days of treatment over 5 days.*

Key points on hydroxychloroquine: *RCTs have demonstrated no evidence of benefit from hydroxychloroquine treatment across a range of clinical settings and across a variety of clinical outcomes. These studies have included patients with mild, moderate or severe COVID-19, in hospitalised or non-hospitalised settings and investigated outcomes including mortality, hospitalisation symptom severity and viral shedding. Emerging evidence from*

[1]*Press-releases are used to quickly communicate key trial results to the public, but often do not contain detailed information on the patient population and analysis methods. Limited information is provided to assess study quality and robustness. Preprints 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 press-releases and preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is a greater potential for dissemination of low-quality research.*

large, high-quality, retrospective, observational studies generally support the findings of RCTs.

Key points on lopinavir-ritonavir: *RCTs have demonstrated no reduction in mortality with lopinavir-ritonavir in hospitalised patients with COVID-19, compared with standard of care. Full study reports of key clinical trials are awaited.*

[1] *Press-releases are used to quickly communicate key trial results to the public, but often do not contain detailed information on the patient population and analysis methods. Limited information is provided to assess study quality and robustness. Preprints 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 press-releases and preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is a greater potential for dissemination of low-quality research.*

Table 1: Summary of consensus guidelines on the use of antivirals in COVID-19

New additions to this version of the review are highlighted in yellow

	Remdesivir
World Health Organisation (WHO, 06/07/21)(5)	Conditional recommendation against the use of remdesivir in hospitalised patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.
Infectious Diseases Society of America (updated 25/08/21) (6)	Among hospitalised patients with severe COVID-19, remdesivir is suggested over no antiviral treatment (Conditional recommendation, Moderate certainty of evidence). Severe illness is defined as patients with SpO2 ≤94% on room air. Among patients with COVID-19 on invasive ventilation and/or ECMO, the IDSA panel suggests against the routine initiation of remdesivir (Conditional recommendation, Very low certainty of evidence). Severe illness is defined as patients with SpO2 ≤94% on room air. 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. (Conditional recommendation, Low certainty of evidence). Severe illness is defined as patients with SpO2 ≤94% on room air. Among hospitalised patients with COVID-19 without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir (Conditional recommendation, Very low certainty of evidence) Among hospitalised patients with severe COVID-19 who cannot receive corticosteroids because of a contraindication, baricitinib with remdesivir is suggested rather than remdesivir alone treatment (Conditional recommendation, Moderate certainty of evidence)
American Thoracic Society/European Respiratory Society coordinated International Task Force (updated 29/07/2020) (7)	Suggests remdesivir for hospitalised patients with COVID-19 pneumonia who require supplemental oxygen, including those who are mechanically ventilated.
Surviving Sepsis Campaign (updated March 2021) (8)	For adults with severe COVID-19 who do not require mechanical ventilation, the group suggested using IV remdesivir over not using (weak recommendation). Remark: Remdesivir should ideally be started within 72 hours of positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction or antigen testing. For adults undergoing mechanical ventilation for critical COVID-19, the group suggested against starting IV remdesivir (weak recommendation).
National Institutes of	The Panel recommends against the continuation of remdesivir in hospitalized

Health (NIH, updated 25/08/21) (9)	patients with COVID-19 who are stable enough for discharge and who do not require supplemental oxygen (strong recommendation based on subgroup analyses of randomized trials). Recommended dosing regimen for remdesivir is 200 mg IV once, then 100 mg IV once daily for 4 days or until hospital discharge. Treatment may be extended for up to 10 days if there is no substantial clinical improvement by Day 5. If the patient progresses to more severe illness, the course of remdesivir should be completed. In patients with a renal function of eGFR<30ml/min/1.73m2 remdesivir is not recommended Recommended for hospitalised patients with COVID-19 who require minimal supplemental oxygen (Moderate recommendation based on subgroup analysis of RCT). Recommended in combination with dexamethasone for patients who require increasing amounts of supplemental oxygen (Moderate recommendation based on expert opinion). Where dexamethasone cannot be used baricitinib plus remdesivir can be used (Moderate recommendation based on other randomised trials or subgroup analysis of RCT). For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, non-invasive ventilation, invasive mechanical ventilation or ECMA, the treatment course of remdesivir should be continued. Insufficient data to recommend for or against use in mild or moderate COVID-19. For patients at high risk of disease progression, the use of remdesivir may be appropriate. Not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.
American College of Physicians (ACP, updated May 2021) (10)	Consider remdesivir for 5 Days to treat hospitalized patients with COVID-19 who do not require mechanical ventilation or ECMO. Consider extending the use of remdesivir to 10 Days to treat hospitalized patients with COVID-19 who require mechanical ventilation or ECMO within a 5-Day course. Avoid Initiating remdesivir to treat hospitalized patients with COVID-19 who are already on mechanical ventilation or ECMO.
National Institute for Clinical Excellence (NICE, updated) UK, updated 02/09/21	Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen. The criteria for accessing remdesivir in the UK are outlined in NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with

	COVID-19 (adults and children 12 years and older), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised. Significantly immunocompromised patients are eligible for an extended course of remdesivir (up to 10 days), if agreed following multidisciplinary team assessment Remdesivir should not be initiated in patients who present to hospital more than 10 days after symptom onset. For remdesivir use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy. The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg. Do not use remdesivir for COVID-19 pneumonia in adults, young people and children who are in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.
	Hydroxychloroquine
World Health Organisation (WHO, 06/07/21)(5)	Recommends against use for the treatment of COVID-19, of any disease severity and any duration of symptoms.
Infectious Diseases Society of America (updated 25/08/21) (6)	Recommends against use in patients with COVID-19. (Strong recommendation, Moderate certainty of evidence) Recommends against hydroxychloroquine in combination with azithromycin in hospitalised patients with COVID-19. (Strong recommendation, low certainty of evidence)
American Thoracic Society/European Respiratory Society coordinated International Task Force (updated 29/07/2020) (7)	Suggests not using hydroxychloroquine, except within a clinical trial, for hospitalised patients with COVID-19 pneumonia who require supplemental oxygen, including those who are mechanically ventilated.
Surviving Sepsis Campaign (updated March 2021) (8)	For adults with severe or critical COVID-19, the group recommend against using hydroxychloroquine (strong recommendation).
National Institutes of Health (NIH, updated 25/08/21) (9)	Recommends against the use of chloroquine or hydroxychloroquine, with or without azithromycin, for the treatment of COVID-19 in hospitalised patients, and non-hospitalised patients (Strong recommendation on the basis of one or more randomised trials without major limitations and subgroup analyses of randomised trials)
American College of	Do not use chloroquine or hydroxychloroquine treatment alone or in

Physicians (ACP, updated 30/09/20) (11)	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)
	Lopinavir-ritonavir
World Health Organisation (WHO, 06/07/21)(5)	Recommends against use for the treatment of COVID-19, of any disease severity and any duration of symptoms
Infectious Diseases Society of America (updated 25/08/21) (6)	Recommended against use in hospitalised patients with COVID-19 (Strong recommendation, Moderate certainty of evidence)
American Thoracic Society/European Respiratory Society coordinated International Task Force (updated 29/07/2020) (7)	Excluded from the latest update of the ATS/ERS guidelines
Surviving Sepsis Campaign (published March 2021) (8)	Excluded from latest update
National Institutes of Health (NIH, updated 25/08/21) (9)	Recommends against use of lopinavir-ritonavir and other HIV protease inhibitors for the treatment of COVID-19 in hospitalised and non-hospitalised patients (Strong recommendation based on randomised trials and expert opinion).

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Background to the Rapid Evidence Review

On the basis of preliminary antiviral prioritisation recommendations by the World Health Organisation (WHO), a targeted literature search (Appendix 1) was developed to identify clinical studies reporting the efficacy of remdesivir, hydroxychloroquine/chloroquine, and lopinavir-ritonavir for the treatment of COVID-19 (12, 13). The Evidence Review Group repeats the literature search regularly and completes a rapid critical appraisal of relevant studies at regular intervals. 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.

Randomised controlled trials (RCTs) have the potential to provide the highest level of evidence as their design is less susceptible to bias than other study designs. However, a number of factors including lack of blinding, small sample sizes, lack of intention-to-treat analyses, approach to missing data, early stopping, and choice of the primary endpoint can limit the reliability and relevance of the findings. Observational study designs can be used to retrospectively analyse data on patients to investigate associations between treatment and outcomes in patients with COVID-19. The analysis and interpretation of data from these non-randomised studies is critically dependent on the use of appropriate statistical analysis, including methods of adjustment to minimise the potential for bias and confounding associated with imbalances in baseline characteristics and standard of care. 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. Changes in knowledge and experience accrued during the cohort follow-up as the pandemic progresses, particularly related to supportive treatments, also pose analytical difficulties which are often not accounted for.

Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in press-releases or unpublished scientific manuscripts called “preprints”. Press-releases are used to quickly communicate trial results to the public summary, but often do not contain detailed information on the patient population and analysis methods. As such, an assessment of study quality and robustness of results is typically not possible. Preprints 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 press-releases and 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 Evidence Review Group's critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.

Evidence for the clinical efficacy of remdesivir for COVID-19

Key points:

RCTs have not demonstrated convincing evidence that remdesivir is effective in reducing mortality in COVID-19. Evidence of benefit with remdesivir in recovery-time in patients on supplemental oxygen at baseline is inconsistent. The optimal duration of treatment is also uncertain. Studies have shown no incremental benefit of 10 days of treatment over 5 days. Further evidence from large RCTs are necessary to address uncertainties.

Summary of evidence:

The evidence of efficacy in severe COVID-19 is inconsistent and comes from two double-blind placebo-controlled RCTs, two open-label RCTs and one dose-comparison trial. The open-label WHO-SOLIDARITY study is by far the largest of the studies investigating remdesivir, and found no definite reduction in in-hospital mortality, initiation of ventilation or duration of hospitalisation(14). This is at odds with the largest of the placebo-controlled studies which was stopped early, following interim analysis showing benefit in time to recovery. A smaller study reported no evidence of benefit compared with placebo, though it was under-powered to detect a significant effect (15, 16). Neither placebo-controlled trial was powered to detect a difference in mortality between treatment groups. One open-label RCT in moderate COVID-19 suggests greater clinical improvement versus treatment with standard of care alone, though the clinical significance of this improvement is unclear. A living network meta-analysis (NMA) of results from the four RCTs, based on 7333 participants, was conducted on behalf of the WHO Guideline Development Group(5). On the basis of this analysis, the WHO made a conditional recommendation against the use of remdesivir in addition to usual care. The odds ratio of mortality was 0.9 (95% CI 0.7-1.12), leading the panel to conclude that remdesivir possibly has little or no effect on mortality with low certainty of evidence. The same conclusions were drawn for mechanical ventilation, time to clinical improvement, duration of hospitalisation and duration of ventilation. The optimal duration of remdesivir treatment is also uncertain. Studies have shown no incremental benefit of 10 days of treatment over 5 days. The emerging evidence has formed the basis for marketing authorisation in the EU and the US.

Table 2: Source of clinical evidence for remdesivir in COVID-19

New additions to this version of the review are highlighted in yellow

Author (study name)	Study design	Peer-reviewed (Yes/no)	Publication date

1. Kalil et al (ACTT-2)	RCT	Yes	11/12/20
2. Pan et al (SOLIDARITY)	RCT	Yes	02/12/20
3. Beigel et al (ACTT-1)	RCT	Yes	08/10/20
4. Spinner et al (SIMPLE)	RCT	Yes	21/08/20
5. Goldman et al (SIMPLE-Severe)	RCT	Yes	27/05/20
6. Wang et al	RCT	Yes	22/04/20
7. Ohl et al	Retrospective cohort study	Yes	01/07/21
8. Coppock et al	Retrospective cohort study	Yes	11/06/21
9. Garibaldi et al	Retrospective cohort study	Yes	24/03/21
10. Garcia-Vidal et al	Retrospective cohort study	Yes	06/03/21
11. Mehta et al	Retrospective cohort study	Yes	23/02/21
12. Flisiak et al	Retrospective cohort study	Yes	31/12/20
13. Pasquini et al	Retrospective cohort study	Yes	23/08/20
14. Olender et al	Indirect treatment comparison	Yes	24/07/20
15. Grein et al	Peer-reviewed case series	Yes	10/04/20

Background to remdesivir in COVID-19

From version 15 of this Review onwards, the literature search strategy for remdesivir will restrict the inclusion of observational studies to those with ≥ 100 participants treated with remdesivir. Further details on this restriction to the search strategy can be found in Appendix 1.

Remdesivir received a conditional marketing authorisation in the EU on 3rd July 2020, to fulfil an unmet medical need with less complete data than normally expected. The marketing authorisation holder (Gilead Sciences) were required to 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 EMA is currently evaluating an application to extend the use of remdesivir to include treating adults with COVID-19 who do not require supplemental oxygen. The current 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 has broad spectrum activity against coronaviruses, including SARS-CoV-2, SARS-CoV, and MERS-CoV, Ebola virus and other viruses (17-19). The currently available data on antiviral effects of remdesivir are limited. Remdesivir has shown effective inhibition of SARS-CoV-2 in vitro in human airways epithelial cells and other cell lines, and in preclinical in vivo in non-human

primate studies (20, 21) . Efficacy was previously shown in MERS and SARS-CoV-1 animal models (18, 19). Remdesivir was investigated for the treatment of Ebola virus but was shown to be less effective than alternative agents (22). An extensive clinical safety database exists from its investigational use in trials for the Ebola virus (22).

Numerous clinical trials of remdesivir are ongoing, and five RCTs have published results ((14-16, 23-25) including placebo-controlled RCTs, a dose-comparison RCT and an RCT investigating the combination of baricitinib and remdesivir compared with dexamethasone and remdesivir . Clinical trials comparing remdesivir in combination with other agents, including baricitinib (ACTT 2 trial, NCT04401579) and interferon beta 1a (ACTT 3 trial, NCT04492475) have completed recruitment but further results from the trials are expected to be published in the future.

A living network meta-analysis (NMA) of results from four RCTs, based on 7333 participants, was conducted on behalf of the WHO Guideline Development Group(5). On the basis of this analysis, the WHO made a conditional recommendation against the use of remdesivir in addition to usual care. The odds ratio of mortality was 0.9 (95% CI 0.7-1.12), leading the panel to conclude that remdesivir possibly has little or no effect on mortality with low certainty of evidence. The same conclusions were drawn for mechanical ventilation, time to clinical improvement, duration of hospitalisation and duration of ventilation. A subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The WHO stated that the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes. Given the costs and resource implications associated with remdesivir, consistent with the approach that should be taken with any new drug, the WHO felt the responsibility should be on demonstrating evidence of efficacy, which is not established by the currently available data(5). These conclusions were echoed in a Rapid Collaborative Review of was published by the European Network of HTA Agencies (EUNetHTA) (26). A number of other systematic reviews have also been published (2-4)

Clinical evidence

1. Kalil et al (ACTT-2) Peer-reviewed RCT, 11/12/20

The ACTT-2 study evaluated whether the combination of the JAK inhibitor baricitinib plus remdesivir was superior to remdesivir alone. This combination was postulated following a number of case series showing an improvement in oxygenation and a reduction in inflammatory markers following baricitinib treatment in COVID-19, possibly due to mitigation of the immune response and prevention of a hyperinflammatory state (23).

Hospitalised patients with COVID-19 and evidence of pneumonia were enrolled across 67 trial sites in eight countries, and randomised 1:1 to receive remdesivir at the licensed dose and baricitinib 4mg once daily for 14 days or until hospital discharge (n=515) or remdesivir and placebo (n=518). The primary outcome measure was the time to recovery, defined as reaching category 1, 2, or 3 on an 8-point ordinal scale during the first 28 days. The mean age of the patients was 55.4 years, and 63.1% were male. 68.3% of the population had moderate disease, and 31.7% had severe disease. The median time to recovery was shorter by 1 day among patients who received combination treatment with baricitinib plus remdesivir compared with patients who received remdesivir and placebo (median, 7 days vs. 8 days; rate ratio for recovery, 1.16 (95% CI, 1.01 to 1.32; p= 0.03). The observed benefit of combination treatment was most evident in patients with a baseline ordinal

score of 6 (high-flow oxygen or non-invasive ventilation), among whom the median time to recovery was 8 days sooner with combination treatment than with placebo. Although this was a pre-specified subgroup analysis, the study was not powered to detect a difference in this subgroup and results should be interpreted with caution. The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (HR for death, 0.65; 95% CI 0.39 to 1.09), but this difference was not statistically significant. Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; p=0.03).

The results of the ACTT-2 study in the ITT population for the primary outcome of time-to-recovery, while statistically significant, are modest and have questionable clinical significance, particularly given the lack of clear mortality benefit. The ACTT-2 study is limited by the lack of a control arm without remdesivir, given the uncertainty associated with the efficacy of remdesivir in patients with very severe COVID-19.

2. Pan et al (WHO SOLIDARITY – interim results) Peer-reviewed RCT, 02/12/20

The Solidarity trial is a simple, 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) (27, 28). Interim results were published on 15 October 2020 (14). The trial evaluated the clinical efficacy and safety of four treatment options against standard of care for COVID-19, including remdesivir (intravenous, 200mg on day 0, 100mg daily on days 1-9), lopinavir-ritonavir (oral, 400mg-100mg twice daily for 14 days), interferon beta-1a given with lopinavir-ritonavir until July 4 and alone thereafter (subcutaneous, three doses of 44mcg over 6 days, or intravenous if available for patients on high-flow oxygen, ventilators or ECMO, 10mcg daily for six days), and hydroxychloroquine (oral, 800mg hour 0, 800mg hour 6, 400mg twice daily from hour 12 for 10 days). The primary objective was to assess effects on in-hospital mortality (i.e., mortality during the original episode of hospitalisation; follow-up ceased at discharge) in all

patients and also in those with moderate COVID and in those with severe COVID (subsequently defined as ventilated when randomised). Secondary outcomes included initiation of ventilation and hospitalisation duration. No placebos were used. Four pairwise comparisons of each study drug vs its controls (concurrently allocated the same management without that drug, despite availability) were conducted. From March 22 to October 4, 2020, 11,330 patients were entered from 405 hospitals in 30 countries in all 6 WHO regions, of whom 11,266 (99.4%) were available for ITT analysis (remdesivir n=2750, hydroxychloroquine n=954, lopinavir-ritonavir n=1,411, IFN β n=2063, no study drug n=4088. 81% of patients were under 70 years of age, 62% were male, 25% had diabetes and 8% were already ventilated at the time of enrolment. The Kaplan-Meier estimate of 28-day mortality was 11.8%. Patient characteristics were well balanced for each drug and its controls, including use of corticosteroids and other non-study treatments. No study drug had any definite effect on mortality, either overall or in any subgroup defined by age or ventilation at entry. Death rate ratios were remdesivir RR=0.95, 95% CI 0.81 to 1.11, p=0.50; hydroxychloroquine RR=1.19, 95% CI 0.89 to 1.59, p=0.23; lopinavir RR=1.00, 95% CI 0.79 to 1.25, p=0.97 and interferon RR=1.16, 95% CI 0.96 to 1.39, p=0.11. No study drug appreciably reduced initiation of ventilation in those not already ventilated, or duration of hospitalisation. Analysis of the proportions hospitalised at day 7 showed that treatments scheduled to last >7 days increased the percentages of patients on those treatments remaining in hospital (as expected in an open-label trial), but the lack of differences in the increases across the treatments indicated no appreciable effect in reducing time to recovery. The hydroxychloroquine, lopinavir-ritonavir and IFN β arms of the trial were discontinued for futility on June 18, July 4, 2020 and October 16 2020, respectively (14).

The SOLIDARITY trial has a number of limitations. Due to its simple design, standard of care and other aspects of patient management were defined locally and may have differed across the 100s of participating sites. The primary outcome, in-hospital mortality, without subsequent follow-up, may miss discharges against hospital advice to avoid the costs of hospitalisations (less likely in the countries included in the Solidarity trial, compared to low-middle-income countries), discharges in anticipation of dying at home (less likely in the case of a highly infectious disease), and discharge with subsequent readmission and death. All-cause mortality at hospital discharge or at 60 days is included in the WHO proposed core outcome measure set for clinical studies of COVID-19 (29). The secondary outcomes, initiation of ventilation and hospitalisation duration, could have been influenced by the study's open-label design as management strategies impacting these outcomes are at the discretion of the investigator, who was aware of treatment assignment. These outcomes may also be influenced by resource availability, which is also likely to have differed across trial sites. Detailed data on disease severity was not collected. The only protocol-specified subgroup analysis considered patients with moderate or severe (i.e. already ventilated) disease at enrolment.

3. Beigel et al (ACTT-1) Peer-reviewed RCT, 08/10/20

The final report from a double-blind RCT of remdesivir in COVID-19 (ACTT-1) was published on 08th October 2020, following an initial press release and preliminary report of interim results from the NIH on April 29th 2020 (15, 30). 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) (31). 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, 1,062 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.

The mean age of patients was 58.9 years and 64.4% were male. The majority of patients were enrolled in North America (79.8%) or Europe (15.3%). Most patients had two or more (54.5%) of the pre-specified coexisting conditions at enrolment, most commonly hypertension (50.2%), obesity (44.8%), and type 2 diabetes mellitus (30.3%). The median time between symptom onset and randomisation was 9 days. Most patients (90.1%) had severe disease at enrolment. A glucocorticoid was received by 21.6% and 24.4% of patients in the remdesivir and placebo arms respectively. Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days vs 15 days; rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001). Benefit was most pronounced for patients with an ordinal score of 5 at baseline (i.e. unplanned subgroup analysis including patients requiring supplemental oxygen, but not high-flow oxygen or non-invasive/invasive ventilation or ECMO) (rate ratio for recovery 1.45, 95% CI, 1.18 to 1.79). 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. Mortality was numerically lower in the remdesivir group than in the placebo group by day 29, but the difference was not significant (hazard ratio for death, 0.73; 95% CI, 0.52 to 1.03). The largest difference in mortality was

observed in patients with a baseline ordinal score of 5 (unplanned subgroup analysis 4.0% vs 12.7%, HR 0.30; 95% CI 0.14 to 0.64). Serious adverse events occurred in 24.6% and 31.6% of patients in the remdesivir and placebo groups, respectively (15).

Early unblinding of treatment assignment led to unblinding of data on 51 patients (4.8% of the study population), and crossover of 26 patients in the placebo group to remdesivir. Sensitivity analyses evaluating the impact of unblinding and crossover produced similar results to the primary analysis. Sensitivity analyses in which data were censored at the earliest reported use of glucocorticoids also showed similar results. Of some concern is a change in the primary outcome mid-trial, as observed from a comparison of study record changes on Clinicaltrials.gov (31). 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 (15). 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.

4. Spinner et al (SIMPLE) Peer-reviewed RCT, 21/08/20

A randomised, open-label trial investigated the efficacy of a 5-day or 10-day course of remdesivir compared with standard of care in hospitalised patients with moderate COVID-19 pneumonia (radiographic evidence of pulmonary infiltrates and SpO2 >94%), at 105 hospitals in the United States, Europe, and Asia (24). Patients were recruited from March 15 to April 18, 2020. Results of this study were initially published in a press-release from Gilead Sciences on 01/06/20, using the study-name “SIMPLE” (32). Patients were randomised in a 1:1:1 ratio and treated with up to 5 days of remdesivir (n=193), up to 10 days of remdesivir (n=191) or standard of care (n=200). Both patients and investigators were aware of open-label treatment assignment. Remdesivir was given at a dose of 200mg intravenously on day 1, followed by 100mg once daily for the subsequent days. Patients who had sufficiently improved in the judgment of the investigator could be discharged from the hospital before finishing their assigned course of treatment. The primary endpoint was clinical status assessed by a 7-point ordinal scale on Day 11. Categories on the ordinal scale ranged from death to not hospitalised, through various degrees of ventilation/oxygenation. Objective criteria for the categorisation or discharge were not defined. The trial was initially designed to investigate the time to discharge as the primary endpoint. This change is reported by the authors to have been made at the start of study enrolment (March 15th), however this

change was only listed on clinicaltrials.gov on April 6th, despite the listing of other changes on numerous occasions throughout late March and early April (33).

The median age of the cohort was 56-58 years, and 60-63% were male. Baseline demographic characteristics were similar between groups. 56% of the cohort had cardiovascular disease, and 40% of the cohort had diabetes. The majority of patients did not require supplemental oxygen at baseline, though 15% of patients deteriorated and required supplemental oxygen between enrolment and treatment initiation. The groups differed in the level of concomitant medication use with significantly greater proportions of patients in the standard care group receiving other investigational agents including hydroxychloroquine, lopinavir-ritonavir and azithromycin over the study follow-up. The median duration of symptoms before treatment initiation was 8-9 days. 91% of patients completed the study through day 28. The last available clinical status was used impute clinical status on day 11 for 37 patients (6.3%), most of whom were transferred to another facility before day 11. A complete course of treatment was received by 76% of patients in the 5-day group (median 5 days) and 38% of patients in the 10-day group (median 6 days). Patients in the 5-day remdesivir group had significantly higher odds of having a better clinical status distribution compared with standard care alone (odds ratio, 1.65; 95%CI, 1.09-2.48;P = .02).There was no significant difference in the primary outcome between the 10-day remdesivir group and the standard care group. There was no difference between either remdesivir group and standard care in any secondary end-point analysis including mortality, duration of oxygen therapy or hospitalisation. Kaplan-Meier estimates of all-cause mortality ranged from 1%-2% across treatment groups. Nausea, hypokalemia and headache were more frequent among remdesivir-treated patients compared with standard care.

There are a number of limitations associated with this study, primarily related to its open-label design and choice of primary endpoint. Firstly, the various categories on the ordinal scale used for the primary endpoint do not have the same clinical significance, leading to uncertainty in the clinical relevance of a “better clinical status distribution”. Secondly, while an ordinal scale for classifying patient response has been proposed by the WHO and has been used in other diseases such as influenza, unbiased effect estimates are only possible if the study is unambiguously double-blinded (34). In this study, management strategies related to hospitalisation, oxygenation and ventilation were at the discretion of the investigator, who was aware of treatment assignment. Patients were not stratified by site at enrolment. Assessment of outcomes that reflect decisions of the investigators is likely to be influenced by knowledge of intervention received. This is particularly important when preferences or expectations regarding the effect of the experimental intervention are strong (35). Moreover, some of these decisions may have been affected by variability in capacity across the 105 hospitals participating in the study. The primary endpoint is therefore considered to be at considerable risk of bias. Finally, regarding the protocol change in primary outcome, it is not clear from the available information to what extent investigators were aware of emerging study results at the time of the protocol change. A significant

protocol change mid-study, particularly given the open-label design of study, could introduce critical bias.

5. Goldman et al (SIMPLE-Severe) Peer-reviewed RCT, 27/05/20

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.

The median age of the cohort was 61-62 years, and 60-68% were male. 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). 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.

6. Wang et al Peer-reviewed RCT, 29/04/20

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 (16). 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 (16). 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 (36). 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 out ruled (16).

7. Ohl et al — Peer-reviewed retrospective cohort study, 01/07/21

This retrospective, multicentre, cohort study examined the associations between remdesivir treatment and survival and length of hospital stay among US veterans hospitalized with COVID-19(37). The primary endpoints of the study were time to all-cause mortality within 30 days of remdesivir treatment (or 30 days of the corresponding hospital day at the time of matching for controls) and time to hospital discharge. Data from the Veterans Health Administration was used to identify 7,388 adult patients across 123 hospitals who were admitted with COVID-19 between May and October 2020. Of these 5,898 were deemed eligible for study inclusion and propensity score matching of patients treated with remdesivir (n=1172) to control patients not treated with remdesivir (n=1172) was used to create the final cohort of 2,344 patients for analysis. Risk adjustment variables included age, sex, race, comorbidities, mechanical ventilation use, ICU admission, laboratory values, vital signs and concurrent mediations.

Patients treated with remdesivir and their matched controls had similar baselines characteristics with standardized differences of less than 10% for all measures. The majority of participants were white (56%) males (94%) with a mean age of 67.8 and 67.0 years in the two groups. A similar proportion of patients in the remdesivir treatment group (12.2%) compared with controls (10.6%) died within 30 days of matching (adjusted HR 1.06; 95% CI, 0.83 to 1.36). Mortality at 30 days was also similar among the subgroups of patients receiving and not receiving dexamethasone treatment at remdesivir initiation, and in sensitivity analysis comparing patients who initiated remdesivir treatment within 48 hours of admission with matched controls who did not initiate remdesivir treatment within 48 hours. Patients who received remdesivir had a longer median time to hospital discharge compared with controls (6 days vs 3 days respectively, $p<0.001$).

This study is limited by its retrospective observational design. While propensity score-matching ensured patients receiving remdesivir treatment were matched with controls with similar illness severity residual confounding could still be an issue. Some key information, such as amount of supplemental oxygen used, was unavailable from the datasets used. The results of the study only pertain to a proportion of patients receiving remdesivir from the original cohort (49.5%) who were able to be matched to controls. This subset of included remdesivir patients had less severe illness compared to those treated with remdesivir who were unmatched and excluded from the analysis. As such, the analysed cohort may not reflect the typical COVID-19 patients receiving remdesivir with regards to illness severity.

8. Coppock et al — Peer-reviewed retrospective cohort study, 11/06/21

This retrospective, multicentre US cohort study aimed to evaluate whether medication related practice patterns and measured patient characteristics in COVID-19 patients explained the decline in mortality seen early in the pandemic (38). The primary outcome was mortality during admission with association of mortality and medication treatment patterns and changes to mortality rates over time explored. The health records of 4,351 patients hospitalized with COVID-19 across 11 inpatient facilities in Pennsylvania and New Jersey between March – July 2020 were examined for this study. Several medications were evaluated with a treatment combination variable created based upon the usage patterns of five primary medications - anticoagulants, corticosteroids, hydroxychloroquine, remdesivir and tocilizumab. Other covariates of interest included age, gender, race, length of stay, level of care, respiratory support/oxygenation, and comorbidities such as coronary artery disease/myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, liver disease, diabetes, renal disease, cancer, metastatic carcinoma, and human immunodeficiency virus infection. Multivariable logistic regression was used to identify predictors of mortality for the overall population and logistic models using a backward selection process for covariates for both non-ICU admissions and ICU admissions evaluated mortality for patients by severity of illness.

The average inpatient mortality rate for the entire period was 15.3% but overall mortality declined significantly from 21.3% in March 2020 to 8.8% in July 2020. With regards to the results of remdesivir usage, for the overall population, the use of anticoagulation and remdesivir (OR 0.25, p=0.0031) and anticoagulation, corticosteroids and remdesivir (OR 0.42, p=0.026) had significant negative correlation estimates for mortality. These treatment combinations, anticoagulation and remdesivir (OR 0.07, p=0.002) and anticoagulation, corticosteroids and remdesivir (OR 0.07, p=0.014), were also associated with lower mortality amongst non-ICU patients. The same pattern was not seen in ICU patients.

This study is limited by its retrospective observational design. Datasets were limited by the lack of information on a number of patient variables such as occupation, household income and residence in a congregate setting such as a nursing home, which could confound the results. Important clinical variables, such as duration of symptoms at the time of presentation and degree of hypoxia, which may help to predict mortality were also absent. In addition, no information regarding treatment course, dose or timing for any of the medications was captured.

9. Garibaldi et al — Peer-reviewed retrospective cohort study, 11/06/21

This retrospective, comparative effectiveness, multicentre, US cohort study examined the association of remdesivir administration with clinical improvement in COVID-19 patients (39). The primary endpoint was time to clinical improvement (defined as discharge alive from hospital without worsening of WHO disease severity score of at least a 2 point decrease in WHO severity sore during hospitalization with 28 days) from the start of remdesivir treatment. A cox proportional hazards regression model was applied with demographic characteristics (e.g. age, gender, race), clinical variables (e.g. supplemental oxygen, vital signs, presence of chronic disease) and laboratory results (e.g. blood count, c-reactive protein) included based on clinical interest and knowledge. A time-dependent propensity score matched pairs of individuals (1 patient treated and another similar untreated patient).

Of the 2483 patients admitted with COVID-19 across the 5 centres between March-August 2020, 2299 were eligible for inclusion with 14.9% receiving remdesivir. 570 matched individuals were included in the analysis with baseline characteristics were well matched between patients and controls. In the Cox proportional hazards regression models, remdesivir treatment was associated with significantly shortened time to clinical improvement compared to controls (5 days for those on treatment compared to 7 days or controls with an adjusted HR 1.47; 95% CI, 1.22 to 1.79). Remdesivir patients with oxygenation of breathing ambient air or nasal cannula oxygen (adjusted HR 1.41; 95% CI, 1.12-1.79) and those with severe disease requiring higher levels of respiratory support (adjusted HR 1.59; 95% CI, 1.02-2.49) also benefitted in the time to clinical improvement compared with matched controls. Remdesivir recipients also had a 28-day mortality rate of 7.7% compared with 14.0% for matched controls but the result did not reach statistical significance. No significant mortality benefit associated with remdesivir treatment with patients with mild to moderate disease or those with severe disease was demonstrated.

This study is limited by its retrospective observational design. While the matched pairs were similar for measured baseline characteristics they were limited by the lack of information on a number of patient variables such as occupation, household income and socioeconomic status, which could confound the results.

10. Garcia-Vidal et al — Peer-reviewed retrospective cohort study, 11/6/21

This retrospective, single-centre, cohort study aims to provide a descriptive report of use of remdesivir by COVID-19 patients in a Spanish hospital between July and September 2020(40). Of the 242 admitted adult COVID-19 patients 50.8% received remdesivir. The remdesivir patients were mostly male (61%) with a median age of 58 years. Most had chronic diseases ranging from hypertension (40.7%) and diabetes (22%) to haematological disease (6.5%) and HIV (2.4%). The median number of days from symptoms onset to hospital admission and to commencing remdesivir treatment was 6 and 7 days respectively.

The majority were treated with other concurrent medication such as dexamethasone (57%), ceftriaxone (42.8%) and tocilizumab (26.8%). The median length of hospital stay was 8 days, with 24% requiring ICU admission and 9% requiring mechanical ventilation. The 30-day mortality rate was 5%. No patient required discontinuation of remdesivir.

This study is limited by its retrospective and descriptive design. Accurate conclusions on the use of remdesivir cannot be made due to the study design limitations and the lack of a comparative control group.

11. Mehta et al — Peer-reviewed retrospective, cohort study, 23/08/20

This retrospective, single-centre, cohort study examined the impact of the timing of remdesivir initiation (symptom onset to remdesivir treatment [SORT] interval) on clinical outcomes in patients with moderate-to-severe COVID-19(41). The primary end-point was the impact of the SORT interval on in-hospital all-cause mortality in patients with moderate-to-severe COVID-19. Patients who attended a single-centre dedicated COVID-19 hospital in Bangalore, India between June and October 2020 were eligible for inclusion if they had confirmed COVID-19 infection, radiologic evidence of pneumonia, peripheral oxygen saturation (SpO2) of <94% and were receiving in-patient treatment for remdesivir. Treatment with remdesivir was a day 1 loading dose of 200mg, followed by a maintenance dose of 100mg daily for 5-10 days, with only patients receiving a 5 dose minimum included in the analysis. Patients were defined as having moderate disease if there was presence of hypoxia (SpO2 <94%, range: 90%–94%) while breathing room air and respiratory rate ≥24 breaths per minute. Severe disease was defined as presence of clinical signs of pneumonia and one of the following criteria: SpO2 <90% while breathing room air, respiratory rate >30 breaths per minute, heart rate >120 beats per minute, presence of acute respiratory distress syndrome, sepsis, or septic shock. Data on certain demographic parameters, concurrent medication use and clinical and laboratory findings were also available for extraction and analysis.

346 patients with moderate-to-severe disease received the minimum remdesivir treatment during the study time period and were included in the analysis. The majority were male (78.0%) with at least one comorbidity (70.2%) and a median age of 60 years. All patients received corticosteroids alongside remdesivir treatment with 37.9% also receiving convalescent plasma and 10.7% receiving tocilizumab. Approximately a third (31.5%) were defined as having moderate disease with the remainder (68.5%) being treated for severe disease. Patients with moderate disease were more likely to be discharged (97.2%) and less likely to die (2.8%) compared with those patients with severe disease (69.2% discharged, 30.8% died).

Kaplan–Meier plots demonstrated significant difference in the probability of survival for SORT interval ≤9 days compared with >9 days (p = 0.03); but not for the other intervals. Based on this, these two subgroups of SORT intervals (≤9 and >9 days) were further analysed to evaluate the impact of the timing of remdesivir initiation. The two SORT interval groups (≤9 and >9 days) were similar for age, sex and presence of commodities, however all-cause mortality was significantly lower in the former compared with the latter group (18.1% and 33.7% respectively; p = 0.004). The odds of death was also significantly lower in patients with SORT interval ≤9 days compared with >9 days (OR = 0.43; 95% CI, 0.25 to 0.75, p = 0.003).

The retrospective study design and lack of a comparative control group really limit the conclusions which can be drawn from these results. In addition, demographic, clinical and laboratory data for analysis was limited by what had been collected at the time of treatment and the study did not consider the optimal duration of remdesivir treatment.

12. Flisiak et al — Peer-reviewed retrospective cohort study, 21/12/20

The SARSTer study is an on-going, retrospective, multicentre, Polish cohort study aimed to evaluate the effectiveness and safety of remdesivir use in patients with COVID-19 in a real-world setting(42). The primary endpoint of the study was clinical improvement as expressed by the WHO ordinal scale which was modified to fit the specificity of the national healthcare system. Improvement was defined as a 2 point decrease on the scale from baseline at day 7, 14, 21 and 28 of hospitalization. Participants were selected from the SARSTer database which includes the details of 1496 patients treated at 30 different Polish centres between March and August 2020. 333 patients in the database were in receipt of one of two antiviral treatments, remdesivir (n=122) and lopinavir-ritonavir (n=211), which due to its reported effectiveness was selected as a control, and were analysed for the purposes of this research. Remdesivir was administered with a 200mg loading dose, followed by a once daily maintenance dose of 100mg for 5-10 days. Lopinavir-ritonavir was administered at a dose of 400/100mg every 12 hours for up to 28 days.

The study participants were balanced in terms of baseline demographic characteristics with the majority of the participants being male (62%) with a mean age of 56.1 and 58.7 years in the two groups. The prevalence of co-morbidities was higher in the remdesivir treatment group, with the difference in ischemic heart disease reaching significance (14% in the remdesivir group compared with 6% in the lopinavir-ritonavir group). Additional medications prescribed during COVID-19 treatment also differed significantly between the two groups with the remdesivir treatment group more frequently being prescribed dexamethasone, convalescent plasma and low-molecular-weight heparin, and the lopinavir-ritonavir treatment group more frequently administered chloroquine and azithromycin. The rate of patients discharged from hospital was similar between the two groups on day 7 and

14 but increased in patients treated with remdesivir on day 21 and 28. While the proportions of ordinal-scale categories were balanced between the treatment groups at baseline significant differences of 15% and 10% between the groups demonstrating clinical improvement in the remdesivir group was seen at day 21 and 28 respectively. There was a significant difference in adverse events between the groups with the lopinavir-ritonavir treatment group experiencing 19% more adverse effects compared with the remdesivir group. Logistic regression analysis showed only remdesivir use was independently associated with a 2-point clinical improvement between baseline and day 21.

This study has a number of limitations which impact the generalizability of its results. The retrospective observational design of the study is a significant limitation. Additionally, the lack of a standard control comparative group, coupled with some significant differences between the two treatment groups at baseline and in concurrent treatments is a concern. The key endpoint was clinical improvement based on a modified version of the WHO ordinal scale, which was tailored to local needs and may be less applicable in other settings. Patient data was retrospectively submitted to the SARSTer database which could lead to considerable bias and/or error.

13. Pasquini et al — Retrospective, observational cohort study, 23/08/20

A retrospective, observational cohort study compared the clinical outcomes of 25 critically ill patients treated with remdesivir, with 26 critically ill patients who did not have access to remdesivir, in a hospital in Pesaro, Italy (43). All patients were admitted to the ICU from 29 February to 20 March, had severe respiratory failure and needed mechanical ventilation at the time of admission. Patients who died within the first 48 hours after ICU admission were excluded from the study. At the time of the study, remdesivir was available only through request for compassionate use from the pharmaceutical company according to specific criteria which included confirmed SARS-CoV-2 infection and the need for mechanical ventilation. Exclusion criteria were creatinine clearance under 30mL/min, serum levels of ALT or AST more than five times the upper limit of the normal range and need for inotropic support. Patients in the remdesivir group received treatment under the compassionate use programme. Patients in the no-remdesivir group did not have access to treatment. The primary outcome was mortality at the end of follow-up, evaluated using the Kaplan-Meier method and compared using the log-rank test. A cox regression model was used to identify independent predictors of outcome.

The median age was 67 years and 92% were male. The median time since symptom onset and treatment was 18 days. The median time from ICU admission to treatment was 7 days. Hypertension and diabetes were present in 55% and 14% of the cohort respectively. Hydroxychloroquine or lopinavir-ritonavir was used in 65% and 57% of the cohort, respectively. Patients in the no-remdesivir group had a higher median SOFA score at

admission (median 5 vs 4 p=0.037, indicating greater risk of morbidity and mortality), had higher rates of renal replacement therapy due to kidney failure, and had higher rates of heart failure and COPD than the remdesivir group. Significantly more patients in the remdesivir group received tocilizumab (28% vs 8%). At the end of follow-up 38 patients (74.5%) had died, 9 patients (17.6%) had been discharged from hospital and 4 patients (7.8%) were still hospitalised but not ventilated. Kaplan–Meier estimates of mortality were significantly lower among patients treated with remdesivir than in untreated patients (56.0% versus 92.3% p< 0.001).

This study is associated with significant bias in favour of remdesivir, which severely limit the credibility of the results. Selection bias is likely to be present as patients with renal impairment or receiving inotropic support, potentially indicating more severe illness, were not eligible for remdesivir treatment. Patients who did not receive remdesivir had greater risk of morbidity and mortality at baseline, according to the SOFA score. In addition, patients in the no-remdesivir group had higher levels of co-morbidity. This selection bias is likely to have biased survival estimates in favour of remdesivir. Retrospective studies of this nature are at critical risk of immortal-time bias, as patients were assigned to groups on the basis of treatment/no-treatment, but treatment wasn't provided until 7 days after ICU admission. Patients in the remdesivir arm, by definition, must have survived until this point, while patients in the no-treatment group are at risk of mortality from the start of follow-up. Study numbers were very low and it is unlikely that a difference in mortality, if it exists, was detectable, given the challenges in demonstrating this effect in much larger COVID-19 RCTs. In order to compare groups in an unbiased manner, it is necessary that both groups are managed in a similar way in every respect except remdesivir treatment. The authors state that the study was undertaken at a time of extreme stress on ICU capacity, during the first three weeks of the pandemic, when the initial need for ventilators, doctors and specialized nurses was largely unmet. In these circumstances, it is unclear whether the consistency of care in terms of management and interventions, necessary to make a valid comparison between groups, could be maintained.

14. Olender et al — Peer-reviewed indirect treatment comparison, 24/7/20

A comparative analysis of data from the Phase 3 SIMPLE-Severe trial (a randomised, phase 3, open-label study comparing two courses of remdesivir, discussed above) and data from a real-world retrospective cohort of patients with severe COVID-19 treated with standard-of-care, was conducted by Gilead Sciences, the sponsor of both studies and developer of remdesivir (44). The cohort study was conducted at 16 sites in the USA, UK, Belgium, Singapore and South Korea. Patients received standard-of-care according to local clinical practice between 06 February and 10 April 2020. The inclusion criteria of the cohort study were designed to align with those of the RCT including SARS-CoV-2 infection confirmed by PCR, SpO2 of ≤94% on room air or requiring supplemental oxygen, with radiographic

evidence of pulmonary infiltrates. However, the exclusion of 392/1268 patients from the retrospective cohort study suggests some significant differences in the inclusion criteria. Interim data from both studies were compared in a pre-specified analysis with a primary endpoint of recovery on day 14, based on the 7-point ordinal scale: improvement to a score of 5 to 7 for baseline of 2-4, 6 or 7 for baseline score of 5, and 7 for baseline score of 6. Propensity score methods were used to increase the comparability of the non-randomised groups, including the following observed baseline characteristics as the independent variables: age, gender, race, region (US, Ex-US), obesity, medical history (yes versus no for hypertension, cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and asthma), medications used to treat COVID-19, and baseline clinical status (7-point ordinal scale). The stabilised IPTW method was used after trimming the patients in either cohort whose propensity scores fell out of the common support region of the propensity score distribution. Baseline characteristic were balanced between the groups after propensity score weighting, with the exception of COPD (absolute standardised difference=0.2) and hydroxychloroquine use. In a scenario including hydroxychloroquine in the propensity score, a number of important factors were imbalanced.

298/397 patients in the remdesivir RCT were included and 816/1268 patients from the non-remdesivir retrospective cohort study were included. The remdesivir group excluded 77 patients enrolled from Italy, patients with trimmed propensity scores and 7 patients with missing data. The non-remdesivir group excluded 392 patients who were not compatible with the RCT due to ECMO, ALT/AST >5ULN or pregnant/breastfeeding, 77 with missing data, 36 with trimmed propensity scores and 7 with baseline ordinal scale assessment of 1 or 6.

At day 14, after IPTW, 74.4% of patients in the remdesivir-cohort versus 59.0% in the non-remdesivir-cohort reached the primary recovery endpoint (OR 2.03, 95% CI 1.34 to 3.08, p<0.001). Remdesivir was associated with a 62 % reduction in the risk of mortality (7.6% vs 12.5%, adjusted OR 0.38, 95% CI 0.22 to 0.68, p=0.001). Results of the sensitivity analysis that included hydroxychloroquine in the propensity score yielded similar results.

This analysis has a number of limitations. The open-label nature of the remdesivir RCT is associated with bias, particularly with regard to the primary outcome which is dependent on decisions of the investigators which are likely to be influenced by knowledge of intervention received. The comparison in this analysis was not randomised, and despite the use of IPTW methods, there may be remaining unobserved imbalances between the groups. This is particularly notable with respect to hydroxychloroquine use, which was imbalanced between groups before and after weighting. While the use of hydroxychloroquine itself may not be expected to impact on the results of the analysis, based on the lack of efficacy observed in hydroxychloroquine studies, imbalances associated with its use may indicate unobserved imbalances in other patient factors. The groups were described as coming from studies with similar enrolment criteria, however the exclusion of 392/1268 patients from

the retrospective cohort study suggests some significant differences in the inclusion criteria. The authors do not report the identity of individual study sites, or if there was overlap between groups. Any overlap would raise questions as to why certain patients were recruited into one study and not the other. Standard-of-care was not standardised across the study sites included in the non-remdesivir group.

15. Grein et al — Peer-reviewed case series, 10/04/20

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 (36). 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.

Evidence for the clinical efficacy of hydroxychloroquine for COVID-19

Key points:

RCTs have demonstrated no evidence of benefit from hydroxychloroquine across a range of clinical settings and across a variety of clinical outcomes. These studies have included patients with mild, moderate or severe COVID-19, in hospitalised or non-hospitalised settings and investigated outcomes including mortality, hospitalisation, symptom-severity and viral shedding. Emerging evidence from large, high-quality, retrospective, observational studies, is inconsistent but generally support the findings of RCTs.

Summary of evidence:

Emerging evidence is increasingly showing a lack of benefit of hydroxychloroquine for the treatment of COVID-19. This follows on from studies published early in the pandemic which reported inconsistent findings, but which were often limited by small sample sizes, unclear methods, unadjusted analyses and sub-optimal reporting. Evidence for hydroxychloroquine in COVID-19 is available from ten peer-reviewed RCTs and a number of retrospective, observational cohort studies, press-releases and case-series. Three of the largest international trials of antivirals for COVID-19, the WHO SOLIDARITY, the UK RECOVERY trial and the US ORCHID trial stopped enrolling patients to the hydroxychloroquine arm of the studies, following interim results which showed no clinical benefit(14, 45, 46). 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 (47).

A lack of meaningful virological or clinical benefit was robustly demonstrated in RCTs of non-hospitalised patients with mild COVID-19 symptoms (48, 49). A peer-reviewed RCT investigating the efficacy and safety of hydroxychloroquine with or without azithromycin in hospitalised patients with mild to moderate COVID-19, demonstrated no difference in clinical status at 15 days (50). In severe COVID-19, three large international RCTs (RECOVERY, ORCHID and SOLIDARITY) have reported finding no significant difference in mortality (14, 45, 46). The potential for confounding exists with earlier, smaller studies due to concomitant therapies and inconsistency between the doses of hydroxychloroquine used.

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. Large, well-

designed retrospective cohort studies have, in general, failed to identify an association between hydroxychloroquine use and mortality (51-53), though this has been inconsistent. A number of smaller studies have also supported RCT findings, though inconsistency is even more common among these studies. The reliability of many retrospective, comparative studies in COVID-19 is limited by the use of inappropriate statistical methodology required to minimise the potential for bias and confounding associated with non-random treatment allocation. 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. Changes in knowledge and experience accrued during the cohort follow-up as the pandemic progresses, particularly related to supportive treatments, also pose analytical difficulties which are often not accounted for. While many of these studies have been peer-reviewed and published in scientific journals, the reliability of this process has been questioned following controversial retractions in high-profile scientific journals (54, 55).

Table 3: Source of clinical evidence for hydroxychloroquine in COVID-19

New additions to this version of the review are highlighted in yellow

Author (study name)	Study design	Peer-reviewed (Yes/no)	Publication
1. Arabi et al	RCT	Yes	12/07/21
2. Réa-Neto et al	RCT	Yes	27/04/21
3. Dubée et al	RCT	Yes	01/04/21
4. Omrani et al	RCT	Yes	20/11/20
5. Horby et al (RECOVERY)	RCT	Yes	09/11/20
6. Self et al (ORCHID)	RCT	Yes	09/11/20
7. Pan et al (SOLIDARITY)	RCT	Yes	02/12/20
8. Abd-Elsalam et al	RCT	Yes	14/08/20
9. Furtado et al	RCT	Yes	04/09/20
10. Calvalcanti et al	RCT	Yes	23/07/20
11. Skipper et al	RCT	Yes	16/07/20
12. Mitja et al	RCT	Yes	16/07/20
13. Tang W et al	RCT	Yes	14/05/20
14. Chen Z et al	RCT	No	30/03/20
15. Chen J et al	RCT	No (abstract)	06/03/20
16. Catteau et al	Retrospective cohort study	Yes	24/08/20
17. Arshad et al	Retrospective cohort study	Yes	01/07/20
18. Sbidian et al	Retrospective cohort study	No	19/06/20
19. Ip et al	Retrospective cohort study	Yes	13/08/20
20. Mahevas et al	Retrospective cohort study	Yes	14/05/20
21. Rosenberg et al	Retrospective cohort study	Yes	11/05/20
22. Carlucci et al	Retrospective cohort study	No	08/05/20

23. Geleris et al	Retrospective cohort study	Yes	07/05/20
24. Mallat et al	Retrospective cohort study	Yes	24/12/20
25. Yu et al	Retrospective cohort study	Yes	15/05/20
26. Magagnoli et al	Retrospective cohort study	Yes	18/12/20
27. Gautret et al	Prospective cohort study	Yes	20/03/20
28. Million et al	Case-series	Yes	05/05/20
29. Molina et al	Case-series	Yes	28/03/20
30. Gautret et al	Case-series	Yes	11/04/20

Background to hydroxychloroquine in COVID-19

From version 14 of this Review onwards, the literature search strategy for hydroxychloroquine will be restricted to peer-reviewed RCTs enrolling greater than 150 patients. Further details on this restriction to the search strategy can be found in Appendix 1.

Hydroxychloroquine is an antimalarial drug with several pharmacological actions which impart therapeutic efficacy primarily in the treatment of rheumatic disease (56). 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 (34). It is unlicensed for the treatment of COVID-19. At the time of writing, hydroxychloroquine is more readily accessible than chloroquine in Ireland (57). 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 (20, 58), and a number of sources have identified these drugs as potentially effective treatments for COVID-19 (20, 59). However, while many clinical trials are ongoing, a limited number of completed trials investigating the comparative efficacy of hydroxychloroquine have been published (60-64) (14) 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 (65-67).

A living systematic review and network meta-analysis published in collaboration by the MAGIC Evidence Ecosystem Foundation and the BMJ (including published studies up to August 10th 2020), concluded that hydroxychloroquine may not reduce mortality (low certainty), mechanical ventilation (moderate certainty) or admission to hospital (low certainty) (3). Another living systematic review and meta-analyses, “The Living Project”, (including published studies up to August 7th 2020), concluded that the possibility of

hydroxychloroquine versus standard care reducing the risk of death and serious adverse events by 20% or more, could be excluded (2).

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.

Clinical evidence

1. Arabi et al — Peer-reviewed RCT, 12/07/21

The REMAP-CAP trial is a large ongoing international adaptive platform clinical trial designed to determine the best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings (68). The part of REMAP-CAP reported in this paper was a placebo-control randomized open-label trial examining the impact of treatment with lopinavir-ritonavir, hydroxychloroquine, and combined therapy of lopinavir-ritonavir and hydroxychloroquine compared to no COVID-19 therapy in critically ill adult patients (≥18 years) with confirmed or suspected COVID-19 being treated in ICU with respiratory or cardiovascular organ failure support.

The primary endpoint was a composite ordinal scale of the number of organ support-free days (OSFD). Respiratory and cardiovascular organ support-free days were calculated up to day 32 with a 1.5-day difference considered to be the minimal clinically important difference and death assigned a score of -1.

726 patients were randomized to receive lopinavir-ritonavir (400mg lopinavir, 100mg ritonavir every 12hours for 5-14days) (n=268), hydroxychloroquine (2 loading doses of 800mg 6 hours apart, followed by 400mg every 12 hours for 12 doses) (n=52), combined therapy of lopinavir-ritonavir and hydroxychloroquine (n=29) or placebo (no COVID-19 anti-viral therapy) (n=377). The patients were mostly white (73%) and male (70%) with a mean age across the treatment groups of between 56-61 years. 99.4% of patients were receiving respiratory support (high-flow nasal cannula, non-invasive or invasive ventilation or ECMO) and 19.8% were receiving vasopressor support.

The median organ support-fee days among patients were 4 (-1-15) in the lopinavir-ritonavir treatment group, 0 (-1 to 9) in hydroxychloroquine treatment group, and -1 (-1 to 7) in the combined therapy of lopinavir-ritonavir and hydroxychloroquine group compared with 6 (-1 to 16) in the placebo group. The corresponding median adjusted ORs were 0.73 (95% CI, 0.55 to 0.99) for the lopinavir-ritonavir treatment group, 0.57 (95% CI, 0.35 to 0.83) for the hydroxychloroquine treatment group, and 0.41 (95% CI, 0.24 to 0.72) for the combined therapy of lopinavir-ritonavir and hydroxychloroquine group when compared to placebo. All

three interventions decreased hospital survival compared to control, with the corresponding median adjusted ORs of 0.65 (95% CI, 0.45 to 0.95), 0.56 (95% CI, 0.36 to 0.89) and 0.36 (95% CI, 0.17 to 0.73) respectively, yielding high probabilities of harm (98.5%, 99.4% and 99.8% respectively). Serious adverse events were reported in 5.1% of patients randomized to receive lopinavir-ritonavir, 6% to receive hydroxychloroquine, 3.7% to receive combined therapy of lopinavir-ritonavir and hydroxychloroquine and 3.3% in the control arm.

The REMAP-CAP is a well conducted trial, designed to demonstrate robust clinically meaningful outcomes. However, the open-label nature of the trial is a limitation although it was mitigated somewhat by neither clinical staff nor the trial steering committee having access to aggregate patient outcomes. Enrolment in the hydroxychloroquine and combination therapy arms was halted on July 13, 2020 based on published concerns regarding the safety and efficacy of hydroxychloroquine. Enrolment into the lopinavir-ritonavir arm was halted on November 19, 2020, after reaching the pre-specified futility threshold.

2. Réa-Neto et al — Peer-reviewed RCT, 27/04/21

The CEPETI is a multicentre, open-label, randomized control trial conducted in six hospitals in Curitiba in Brazil examining the impact of treatment with chloroquine or hydroxychloroquine in combination with standard of care compared with standard of care alone in critically ill adult ICU patients (≥18 years) with confirmed or suspected COVID-19(69).

The primary endpoint was clinical status of patients measured on day 14, evaluated by a 9-point ordinal scale recommended by the WHO with the lowest score of 0 being assigned to patients who are non-hospitalized with no clinical or virological evidence of infection and the highest score of 8 assigned to those who were dead.

142 patients were randomized 1:1 within 48hours of admission to the intervention group (n=71) to receive chloroquine (450mg BID on day 1, followed by 450mg once daily for day 2-5) or hydroxychloroquine (400mg BID on day 1, followed by 400mg once daily for day 2-5) in combination with standard of care or to the control group (n=71) to receive standard of care alone. Standard of care was determined by best practice guidelines for the care of critically ill patients with COVID-19 allowing the use of glucocorticoids, antibiotics and antiviral agents.

The patients were mostly male (66.7%) with a median age of 53 years. 81.9% were receiving supplemental oxygen at baseline, with 18.1% mechanically ventilated. By day 14, the proportional odds of being in a worse clinical condition according to the 9-pount ordinal scale was higher in the intervention group compared with the control group (OR 2.45, 95%

CI 1.17 to 4.93, p=0.016). The cumulative incidence of non-intubated enrolled patients requiring mechanical ventilation was higher in the intervention group compared to the control group (RR 2.15, 95% CI, 1.05 to 4.4, p=0.030) as was the cumulative incidence of acute renal dysfunction at any point from randomization until the day 28 (RR 2.24, 95% CI, 1.01 to 4.99, p=0.048). No differences were seen in ventilator-free days or lengths of ICU and hospital stays; and while mortality was numerically higher in the intervention group this difference was not statistically significant.

While the CEPETI trial was generally well conducted trial with clinically meaningful outcomes, it has some limitations. The open-label nature of the trial and lack of measures in place to mitigate the potential bias this could cause is a concern. Patients who were discharged before day 5 self-administered their medication at home. In addition, discharged patients on days 5, 7, 10, 14 and 28 were assessed by telephone survey compared with those who remained in hospital who were assessed clinically via a case-report system. No details on or assessment of the potential impact of these early discharges was provided by the authors. While there were no concerns re the assessed safety outcome measures of arrhythmias and other cardiovascular events, the emerging results for the primary endpoint resulted in the trial being halted before reaching the planned sample size due to harmful effects including a worsening of clinical status, increased risk of renal dysfunction and increased need for mechanical ventilation.

3. Dubée et al — Peer-reviewed RCT, 01/14/21

The HYCOVID study is a multicentre, double-blind, placebo-controlled, randomised trial conducted across 48 hospitals in France and the Principality of Monaco (70). The trial was designed to evaluate the efficacy and safety of hydroxychloroquine in adult patients with mild to moderate COVID-19 who had one of the following risk factors for worsening: need for supplemental oxygen, age ≥75 years, age between 60 and 74 years and the presence of at least one co-morbidity. This study excluded patients who were severely ill requiring oxygen therapy or ICU care.

The primary endpoint was a composite of mortality and the need for invasive mechanical ventilation within 14 days following randomization. Secondary endpoints included the rate of mortality or invasive ventilation by day 28 and clinical evolution evaluated by a 9-point ordinal scale recommended by the WHO with the lowest score of 0 being assigned to patients who are non-hospitalized with no clinical or virological evidence of infection and the highest score of 8 assigned to those who died.

250 patients were randomized 1:1 to the intervention group (n=125) to receive hydroxychloroquine (200mg tablets – two tablets twice daily on day 1, followed by one

tablet twice daily for the remaining 8 days) or to the control group (n=125) to receive placebo (placebo tablets provided as a similar dosing regimen to the intervention group).

Baseline patient characteristics were generally well balanced for demographic and clinical characteristics across the intervention and control group. Males made up 52.0% and 44.8% of each group respectively and the median age was 77 years. No significant difference in the primary endpoint of a composite of mortality and the need for invasive mechanical ventilation within 14 days following randomization was seen between intervention (7.3%) or placebo (6.5%) groups (RR 1.12; 95% CI, 0.45 to 2.80, p=0.82). Similarly no difference in the rate of mortality or invasive ventilation by day 28 was seen between the treatment groups. No difference in the odds of being in a worse clinical condition according to the 9-pount ordinal scale was seen between the intervention and control group. The rate of adverse effects were similar in the two groups.

The HYCOVID study has some significant limitations which limit the generalizability of its results. The trial was halted 2 months after it had started by the French regulatory authority due to reports of hydroxychloroquine toxicity emerging from pharmacovigilance databases and observational studies and the sponsors because of a low inclusion rate due to the slowdown of the pandemic in France. Just 19% of the planned number of patients were included in the study at the time of it cessation leading to a lack of power. As a consequence the results are not adequately powered to make a statement on the efficacy of hydroxychloroquine in patients with mild to moderate COVID-19.

4. Omrani et al — Peer-reviewed RCT, 20/11/20

The Q-PROTECT study was a double-blinded placebo-controlled trial among non-hospitalised patients with mild or no symptoms within one day of COVID-19 positivity, tested by PCR. All patients were enrolled from a quarantine facility for COVID-positive patients who did not require hospitalisation or antiviral therapy according to national guidelines. In practice, this included young, expatriate males who cannot be home-quarantined. The primary endpoint was proportion of virologic cure (no virus detected) cases at day 6. 456 patients were randomised to hydroxychloroquine (600mg daily for one week) (n=152) or hydroxychloroquine+azithromycin (500mg day one, 250mg daily on days two through five) (n=152) or placebo (n=152). 99% of the cohort were male, aged 40-42 years.

Day 6 ITT analysis found no difference in groups' proportions achieving virologic cure: hydroxychloroquine 10.5%, hydroxychloroquine+azithromycin 12.8%, placebo 12.2% p=0.81). There were no serious adverse events

The primary outcome of virologic cure is not a clinical outcome, and provides no insight into the clinical status of the patient but does provide strong evidence of the presence of the pathogen and is accepted as an appropriate outcome by the WHO. The trial population comprised almost all young males with mild or no COVID symptoms, and findings therefore cannot be extrapolated to older patients, females or those with more severe disease.

5. Horby et al (RECOVERY) Peer-reviewed RCT, 09/11/20

RECOVERY is a randomised, open-label trial investigating whether various treatments are beneficial for people hospitalised with suspected or confirmed COVID-19. The trial initially investigated the benefits of lopinavir-ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab, and subsequently dropped a number of arms for futility (71). The trial is conducted at 176 hospitals in the UK. Hospitalised patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection were randomised in a ratio of 2:1 to either usual standard of care or usual standard of care plus hydroxychloroquine (800mg at zero and 6 hours, followed by 400mg twice daily, starting at 12 hours, for the next 9 days or until discharge) or one of the other available treatment arms. Patients with known prolonged electrocardiograph QTc interval were ineligible for the hydroxychloroquine arm. The primary outcome was all-cause mortality, assessed after 28 days, with further planned analysis at 6 months. Enrolment of participants to the hydroxychloroquine arm was closed on 5th June 2020 following a review of data by the independent Data Monitoring Committee which recommended a review of unblinded data on the hydroxychloroquine arm of the study by the chief investigators.

While the hydroxychloroquine arm of the study was open, 1561 patients were randomized to hydroxychloroquine and 3155 were randomised to usual care with the remainder being randomized to one of the other treatment arms (72). Baseline demographics and disease characteristics were well-balanced across treatment groups. The mean age of the cohort was 65.3 years and 38% were female. The mean time since symptom onset was 9 days. 90% of patients had laboratory confirmed SARS-CoV-2 infection. At least one major co-morbidity was present in 57% of the cohort. Diabetes, heart disease and chronic lung disease was present in 27%, 26% and 22% respectively. 17% of patients were receiving mechanical ventilation or ECMO at randomisation, while 60% were receiving oxygen only. Use of azithromycin or other macrolide, and dexamethasone was similar between study arms. There was no significant difference in 28-day mortality between study arms (27.0% hydroxychloroquine vs 25.0% usual care, rate ratio 1.09; 95% CI 0.97 to 1.23; p=0.15). The results were similar across pre-specified subgroups including those who tested positive for SARS-CoV-2. Hydroxychloroquine was associated with a longer time until discharge alive from hospital (median 16 days vs 13 days), and patients on hydroxychloroquine who were not undergoing mechanical ventilation at baseline were more likely to progress to invasive mechanical ventilation or death than patients receiving usual care (30.7% vs. 26.9%; risk

ratio 1.14; 95% CI 1.03-1.27). There were no significant differences in the frequency of major cardiac arrhythmias (72).

RECOVERY is a well-designed study and has reported robust findings on the efficacy of hydroxychloroquine in the enrolled population of hospitalised patients. The fatality rate in the usual care arm is reported as being consistent with hospitalised patient cohorts across the UK and elsewhere. The secondary outcomes of the study, time until discharge and the composite endpoint of initiation of mechanical ventilation or death, could have been influenced by the study's open-label design as management strategies impacting these outcomes are at the discretion of the investigator, who was aware of treatment assignment. The findings cannot be extrapolated to patients with less severe COVID-19, or to the use of hydroxychloroquine as prophylaxis.

6. Self et al (ORCHID) Peer-reviewed RCT, 09/11/20

The ORCHID trial was a multicentre, double-blind, placebo-controlled RCT conducted at 34 hospitals in the US, which randomly assigned patients to hydroxychloroquine (400mg twice daily for 2 doses, then 200mg twice daily for 8 doses) (n = 242) or placebo (n = 237). Adults who were hospitalised for less than 48 hours with laboratory-confirmed SARS-CoV-2 infection and symptoms of respiratory illness for less than 10 days were enrolled. The primary outcome was clinical status 14 days after randomisation assessed with a 7-category ordinal scale, ranging from not hospitalised to death. Trial enrolment was stopped for futility following randomisation of 479 patients after a series of blinded interim analyses.

Baseline characteristics and demographics were similar between treatments. The median age of enrolled patients was 57 years and 44.3% were female. 49.4%-56.2% of the cohort had hypertension, and 32.9%-36.4% had diabetes. 65% of the cohort were receiving supplemental oxygen or on ventilation at the time of randomisation. The median duration of symptoms prior to randomization was 5 days (IQR, 3 to 7 days). Concomitant medicines including remdesivir, azithromycin and corticosteroids were received by similar proportions of patients in each group.

At 14 days after randomization, there was no significant difference in the COVID Outcomes Scale score between the hydroxychloroquine group (median [IQR] score, 6 [4-7]) and placebo group (median [IQR] score, 6 [4-7]) (adjusted OR, 1.02 [95% CI, 0.73-1.42), or between any pre-specified subgroups, or in any of the secondary outcomes including mortality.

The ORCHID trial was a well-conducted study, designed to demonstrate robust, clinically-meaningful outcomes. The findings of the trial cannot be extrapolated to non-hospitalised patients, or patients with shorter duration of symptoms prior to treatment.

7. Pan et al (WHO SOLIDARITY – interim results) Peer-reviewed RCT, 02/12/20

Full details of this study are discussed in the "Evidence for Clinical Efficacy of Remdesivir" section of this review. In summary, in a simple, international, multi-centre, adaptive, randomised, open-label, controlled clinical trial, launched by the World Health Organization (WHO) and partners, evaluated the clinical efficacy and safety of four treatment options against standard of care for COVID-19 in hospitalised patients. The study found that no study drug had any definite effect on mortality, either overall or in any subgroup defined by age or ventilation at entry(14). Death rate ratios were remdesivir RR=0.95, 95% CI 0.81 to 1.11, p=0.50; hydroxychloroquine RR=1.19, 95% CI 0.89 to 1.59, p=0.23; lopinavir RR=1.00, 95% CI 0.79 to 1.25, p=0.97 and interferon RR=1.16, 95% CI 0.96 to 1.39, p=0.11. No study drug appreciably reduced initiation of ventilation in those not already ventilated. Analysis of the proportions hospitalised at day 7 showed that treatments scheduled to last >7 days increased the percentages of patients on those treatments remaining in hospital (as expected in an open-label trial), but the lack of differences in the increases across the treatments indicated no appreciable effect in reducing time to recovery. The hydroxychloroquine arm of the trial was discontinued for futility on June 18 2020 (14).

8. Abd-Elsalam et al Peer-reviewed RCT, 14/08/20

An RCT conducted across three university hospitals in Egypt evaluated the safety and efficacy of hydroxychloroquine added to standard of care versus standard of care alone in hospitalised patients with confirmed COVID-19 (73). 194 patients with confirmed COVID-19 were randomised 1:1 to hydroxychloroquine (400mg twice daily on day 1 followed by 200mg twice daily) plus standard of care, or standard of care alone, for 15 days. Allocation was stratified based on disease severity (mild, moderate or severe). Patients were followed up for four weeks. The primary endpoints were reported to be recovery within 28 days, need for mechanical ventilation, or death, though the statistical plan appears to only have addressed recovery in the power calculation. Standard of care included the following, as required: paracetamol, oxygen, fluids, empiric antibiotic (cephalosporins), oseltamivir and invasive mechanical ventilation with hydrocortisone for severe cases.

The mean age of the cohort was 40.72 years, 58.8% were male, 14.3% had comorbidities. The proportions of patients in each severity-category at baseline were not reported, though there was no significant difference between groups regarding any of the baseline characteristics or laboratory parameters. After 28 days, there was no significant difference between the groups in recovery, mechanical ventilation or death (73).

The study is limited by its small sample size, which was likely insufficient to demonstrate difference in efficacy, if it existed. There is some evidence that dexamethasone may improve mortality in patients with COVID-19 receiving supplemental oxygen and

glucocorticoids are now widely recommended in these patients as a result. Hydrocortisone was included in standard of care for severe cases, though it is not clear how many patients received this treatment or whether this was balanced across treatment groups.

9. Furtado et al

Peer-reviewed RCT, 04/09/20

The efficacy and safety of adding azithromycin to standard of care, which included hydroxychloroquine, in patients with severe COVID-19 was investigated in an open-label randomised clinical trial at 57 centres in Brazil (74). Patents were randomised 1:1 to azithromycin (500 mg once daily for 10 days) plus standard of care or standard of care without macrolides. All patients received hydroxychloroquine (400 mg twice daily for 10 days) as part of standard of care. The primary outcome was clinical status at day 15 on a six-point ordinal scale, assessed by an independent adjudication (with an OR>1 representing a clinical worsening in the azithromycin group versus the control group). The scale ranged from 1=not admitted to hospital, to 6=death. The modified ITT population included patients confirmed SARS-CoV-2 infection, and included 214 patients in the azithromycin group and 183 patients in the control group.

Baseline characteristics were similar across treatment groups. Almost half of patients (49%) were on mechanical ventilation at baseline. The median time from symptom onset to randomisation was 8.0 days (IQR 6-10). The median age was 59.8 years and 66% were male. The primary endpoint was not significantly different between the azithromycin and control groups (OR 1.36 [95% CI 0.94–1.97], p=0·11). Rates of adverse events were also not different between the two groups (74).

Various categories on the ordinal scale used for the primary outcome do not have the same clinical significance, leading to uncertainty in the clinical relevance of a “better clinical status distribution”. The primary outcome is also at risk of bias due to the open-label nature of the study. In this study, if, in the opinion of the investigator, patients had sufficiently improved, they could be discharged from the hospital before finishing their experimental treatment. This procedure, in a study with an open-label design, may bias in favour of the experimental treatment. The effect of azithromycin versus standard of care without hydroxychloroquine cannot be ascertained from this study. However, as growing evidence shows no effect of hydroxychloroquine on clinical outcomes in COVID-19, plausible effects in this context may be hypothesised. The findings of this study are limited to patients with severe COVID-19 and cannot be extrapolated to patients with mild or moderate disease.

10. Cavalcanti et al (Coalition Covid-19 Brazil 1)

Peer-reviewed RCT, 23/07/20

A multicentre, randomised, open-label trial investigated the efficacy and safety of hydroxychloroquine with or without azithromycin in patients with mild to moderate COVID-

19 at 55 hospitals in Brazil (50). Eligible patients were hospitalised with suspected or confirmed Covid-19, with 14 or fewer days since symptom onset and were receiving either no supplemental oxygen or a maximum of 4L/min of supplemental oxygen. Patients were randomised in a 1:1:1 ratio to receive standard care (n=229), standard care plus hydroxychloroquine (440mg twice daily for 7 days) (n=221), or standard care plus hydroxychloroquine plus azithromycin (500mg daily for 7 days) (n=217). The primary outcome was clinical status at 15 days, according to a seven-level ordinal scale which ranged from not hospitalised with no limitations on activities, to death, through various stages of hospitalisation and oxygenation/ventilation. The primary outcome was changed from a 6-level scale to a 7-level scale before the first enrolled patients had reached 15 days of follow-up, allowing the investigators to assess limitations on activities. Data were analysed in the modified-ITT population (m-ITT), including only patients with a confirmed COVID-19 diagnosis.

The mean age of the cohort was 50 years, and 58% were male. 42% of patients were receiving supplemental oxygen at baseline. Hypertension or diabetes was present in 29% and 19% of the cohort, respectively. Demographic and disease characteristics were well-balanced across treatment groups in the ITT and mITT populations. Among patients with confirmed COVID-19, there were no significant between-group differences in the proportional odds of having a higher (worse) score on the seven-point ordinal scale at 15 days (hydroxychloroquine plus azithromycin vs. control: OR 0.99; 95% CI 0.57 to 1.73; p=1.00; hydroxychloroquine alone vs. control: OR 1.21; 95% CI 0.69 to 2.11; p=1.00; and hydroxychloroquine plus azithromycin vs. hydroxychloroquine alone: OR 0.82; 95% CI, 0.47 to 1.43; p=1.00). This was also reflected in the ITT analysis. There were no significant differences in any of the secondary outcomes. The mortality rate was low in the study, 1.7% to 3.1% across the study groups. Adverse events were more common in patients receiving hydroxychloroquine than those who were not receiving it. Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine with or without azithromycin, than in those who were not receiving either agent. However, as ECGs were conducted less frequently in the standard care group, the significance of this finding is unclear.

This study is limited by its open-label design and choice of primary endpoint. The primary endpoint, while similar to that proposed by the WHO and used previously in other similar disease such as influenza, is at considerable risk of bias in an open-label trial. Management strategies related to hospitalisation, oxygenation and ventilation were at the discretion of the investigator, who was aware of treatment assignment. Assessment of outcomes that reflect decisions of the investigators is likely to be influenced by knowledge of intervention received. This is particularly important when preferences or expectations regarding the effect of the experimental intervention are strong (35).

A randomized, double-blind, placebo-controlled trial conducted across the US and Canada from 22/03/20 to 20/05/20 investigated the efficacy of hydroxychloroquine in non-hospitalised adults with COVID-19 (49). Eligible patients had fewer than 4 days of symptoms and either laboratory-confirmed COVID-19, or COVID-19-compatible symptoms and an epidemiologic link to a contact with laboratory-confirmed COVID-19. Healthcare workers with COVID-19-compatible symptoms and high-risk exposure to a contact with pending PCR results were enrolled after symptom review by an infectious diseases physician. Patients who had high-risk exposure and were asymptomatic at the time of consent for a companion post-exposure prophylaxis trial, were also eligible for inclusion in analysis if they became symptomatic before starting treatment. These enrolment criteria were specified to overcome the challenges of limited testing capacity and false-negative results early in the disease course. Patients were enrolled through internet-based surveys and eligibility was determined on the basis of a self-screening survey. Participants were randomised in a 1:1 ratio to receive hydroxychloroquine 800 mg once, then 600 mg 6-8 hours later, then 600 mg once daily for 4 more days (5 days in total) (n=244), or placebo (n=247). The initial primary outcome was an ordinal outcome by day 14 of not hospitalised, hospitalised, or intensive care unit stay or death. The primary endpoint was changed during the study, following interim analysis which showed a much lower rate of hospitalisation or death than expected which would require significantly greater numbers than was attainable in the trial. The final primary endpoint was the change in overall symptom severity on a visual analogue scale ranging from 0 (no symptoms) to 10 (most severe symptoms). Scores were recorded online by participants at baseline and days 3, 5, 10 and 14. The symptom severity score was self-assessed and data was collected using online survey, with direct follow-up where necessary.

The median age of the cohort was 40 years, and 44% were male. No chronic medical conditions were reports by 68% of the cohort. Baseline demographics and symptom profile were similar between groups. 34% of the cohort was PCR positive and 63%-69% of the cohort was exposed to contacts who were PCR positive. Longitudinal data on symptom severity was available for 423/491 (86%) participants, and vital status was available for 465/491 (95%). Change in symptom severity over 14 days didn't differ between groups (relative difference in symptom severity: 12%; absolute difference -0.27 points, 95% CI -0.61 to 0.07 points; p= 0.117). Subgroup results were generally consistent with the overall result. The incidence of hospitalization or death was 3.2% (15/465) among participants with known vital status and did not differ between groups (P = 0.29).

The lack of confirmation of SARS-CoV-2 infection in two thirds of the cohort is a limitation of trial. This was due to the limited supplies of PCR testing in the US at the time and frequent delays obtaining test results. 16% of participants included in the analysis had a confirmed negative result on PCR test – which the authors contend falls within the known false-

negative rate of testing. Follow-up was incomplete for 14% of participants. Findings of this trial are limited to the outpatient treatment of mild COVID-19.

12. Mitja et al — Peer-reviewed RCT, 16/07/20

A multicentre, open-label, randomised, controlled trial, conducted in Spain from 17/03/20 to 26/05/20, investigated the efficacy of early treatment with hydroxychloroquine in outpatients with mild COVID-19 (48). Patients were identified for selection from an electronic registry which included all patients with a positive COVID-19 test in a region covering over 4 million inhabitants. Adults with a positive PCR test for SARS-CoV-2 were eligible if they were non-hospitalised and had mild symptoms of COVID-19. Participants were randomised 1:1 to hydroxychloroquine 800mg on day 1 followed by 400mg once daily for six days (n=136), or no treatment, aside from usual care (n=157). Patients were assessed on day 1, 3, 7, 14 and 28 via a combination of home visits and phone calls. Serial oral and nasopharyngeal swab samples were collected on days 1, 3 and 7. The primary outcome was the reduction of viral RNA load in nasopharyngeal swabs at days 3, and 7 after treatment start. Efficacy was determined by comparing the mean reduction of the viral load from baseline to days 3 and 7. While this was an open-label trial, outcome assessors for the primary outcome were unaware of treatment allocation. The secondary outcomes were clinical progression measured by a simplified 4-point version of the WHO progression scale, and time from randomization to complete resolution of symptoms within the 28-days follow-up period.

Baseline demographics were similar between groups. The mean age of the cohort was 41.6 years and 31.4% were male. The median time from symptom onset to enrolment was 3 days. Any coexisting disease was present in 52%-54% of the cohort. The majority of participants were healthcare nursing home workers (84%-89%). There were no significant differences between the hydroxychloroquine and no-treatment arms in viral load reduction at day 3 or 7. The risk of hospitalisation was similar in the hydroxychloroquine and no treatment-group (5.9% vs 7.1%: RR 0.75, 95% CI 0.32 to 1.77) and there was no difference in the mean time to resolution of symptoms (10 days vs 12 days, p=0.38). No patients required mechanical ventilation or died during the study. 72% of patients in the hydroxychloroquine group experienced at least one adverse event during the 28 days of follow-up, mainly gastrointestinal, compared with 9% of the no-treatment group. No major adverse events relate to treatment were observed.

The study is limited by its open-label design, however the objective nature of the primary outcome and the blinding of outcome assessors mitigates this bias for the primary outcome. Combination treatment with cobicistat-boosted darunavir was included in the original protocol and received by some early-enrolled patients, but was subsequently dropped from

the protocol following external evidence of inactivity. The overrepresentation of healthcare and nursing home workers may limit the generalisability of the study findings.

13. Tang W et al — Peer-reviewed RCT report, 14/05/20

Tang et al conducted a multicentre, open-label RCT to assess the efficacy and safety of hydroxychloroquine in adult patients with COVID-19 (60). 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 (60). 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(60).

14. Chen Z et al Non-peer-reviewed RCT 30/03/20

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 (63). 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) (n=31) or standard treatment plus hydroxychloroquine 400 mg daily for five days (n=31). Patients with confirmed SARS-CoV-2 were included if they were ≥18 years, had pneumonia on chest CT, and had mild respiratory illness (SaO2/SPO2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg). Exclusion criteria included severe or critical illness, retinopathy or other retinal diseases, arrhythmias, among others (63). 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 (63).

This study is limited to patients with mild COVID-19 disease, and has a very short (five-day) follow-up. Patient numbers were very small. 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 (63).

15. Chen J et al RCT Abstract (peer-review status unknown), 06/03/20

An English abstract of a Chinese study reporting the use of hydroxychloroquine in China was published on 6th March 2020 (62). 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 (62).

16. Catteau et al — Peer-reviewed retrospective cohort study, 24/08/20

A retrospective cohort study assessed the association between hydroxychloroquine and in-hospital mortality using data gathered as part of Belgian national surveillance of hospitalised patients with COVID-19(75). Data was collected via two online questionnaires, including information after admission and after discharge. Low-dose hydroxychloroquine (2400mg over five days) was recommended for hospitalised patients with COVID-19 during the analysis period in Belgium. Eligible patients had COVID-19 confirmed by RT-PCR and/or rapid antigen test on respiratory samples, before 01/05/20, and had both admission and discharge questionnaires reported up to 24/05/20. Patients who were discharged (either alive or dead) within 24 hours after hospital admission or before diagnosis confirmation were excluded. All patients having started any COVID-19-related treatment before symptom onset were also excluded. Missing data among important prognostic baseline covariates were assumed to be missing at random. A competing risks proportional hazards regression model, with robust standard errors allowing for clustering within hospitals was used to analyse in-hospital death. Cause-specific hazards of treatment effect were adjusted for baseline covariates, clinical features and time of diagnosis. Sensitivity analyses considered additional adjustments in the model, missing data impact and possible immortal time bias associated with delayed treatment receipt.

The database included 15,544 case records of COVID-19 patients, from 109 Belgian hospitals, of which 8,075 were included in the comparative analysis. The majority of the exclusions were related to the absence of discharge data, or treatment with other specific COVID-19 treatments, including hydroxychloroquine combination treatments. 4,542

patients were included in the hydroxychloroquine group and 3,533 were included in the no-hydroxychloroquine group. 78.2% of patients treated with hydroxychloroquine initiated the treatment within 24 hours after diagnosis. The median age was 71 years and 54.5% were male. In general, patients had severe disease with more than 80% having radiological pneumonia. There were significant differences between the hydroxychloroquine and no-hydroxychloroquine group. Patients who received hydroxychloroquine were younger, had less pre-existing conditions including cardiovascular disease and hypertension. However, they also had more severe disease as evidence by radiographic and clinical features. Incidental use of steroids was very low in both groups, though slightly higher in the hydroxychloroquine group (8.1% vs 5.9% respectively). The overall mortality rate was 21.8% (1,761 /8,075) and was lower in the hydroxychloroquine group than in the no-hydroxychloroquine group (17.7% vs 27.1%, $p<0.001$). The inverse propensity weighted standardised cumulative incidence of in-hospital death was 19.1% with hydroxychloroquine alone, and 26.5% with supportive care only (adjusted HR 0.684, 95% CI 0.617–0.758). This treatment effect was consistent across the early diagnosis (within 5 days of symptoms) and late diagnosis (after 5 days of symptoms) groups, and in sensitivity analyses taking censored data and immortal bias into account. No increased short term risk of cardiotoxicity was observed with hydroxychloroquine treatment.

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. A significant proportion of exclusions related to the absence of discharge data. Comparison of demographic characteristics and pre-existing conditions did not reveal significant differences between patient with and without hospital discharge data, however comparative information of minimal and it is not clear if the analysis set is fully representative of the broader population of patients hospitalised with COVID-19.

17. Arshad et al — Peer-reviewed retrospective cohort study, 01/07/20

A retrospective cohort study evaluated clinical outcomes of all consecutive patients hospitalised with COVID-19 in a six-hospital integrated health system in the US (76) . Protocol-driven treatments in the hospitals included hydroxychloroquine (400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5), hydroxychloroquine + azithromycin, reserved for selected patients with severe COVID-19 and with minimal cardiac risk factors (azithromycin dosed as 500 mg once daily on day 1 followed by 250 mg once daily for the next 4 days), and other treatments for COVID-19. The primary endpoint was in-patient hospital mortality in each treatment group. Multivariable Cox regression models and Kaplan–Meier survival curves were used to compare survival among treatment groups while controlling for baseline demographics and disease severity. Propensity score

matching was also conducted to compare outcomes in mortality across treatment groups. 2,541 consecutive patients were included in the analysis.

The median age was 64 years and 51% were male. Treatment was received by 84% of the cohort (47.3% hydroxychloroquine alone, 30.8% hydroxychloroquine + azithromycin, 5.8% azithromycin alone), and 16.1% received neither treatment. Patients who received neither treatment were older and had lower levels of chronic lung disease than patients who received treatments. Baseline disease severity was not recorded consistently across the cohort. More patients in the treatment groups received steroids and tocilizumab than in the neither-treatment group. Overall crude mortality rates were 18.1% in the entire cohort, 13.5% in the hydroxychloroquine alone group, 20.1% in those receiving hydroxychloroquine + azithromycin, 22.4% in the azithromycin alone group, and 26.4% for neither treatment ($p < 0.001$). In the multivariable Cox regression model of mortality, treatment with hydroxychloroquine alone decreased the mortality hazard ratio by 66% ($p < 0.001$), and hydroxychloroquine + azithromycin decreased the mortality hazard ratio by 71% ($p < 0.001$) compared with neither treatment. Kaplan–Meier survival curves, propensity-matched for hydroxychloroquine status, also showed significantly improved survival among patients in the hydroxychloroquine alone and hydroxychloroquine + azithromycin group compared with groups not receiving hydroxychloroquine and those receiving azithromycin alone (76).

This study is limited by its retrospective, observational design. Although treatments in this study were described as “protocol-driven”, it is not clear what the protocol was or how this may have changed over the course of the follow-up. Important information on baseline disease severity is missing, limiting the scope of the study to fully adjust for confounding by indication. Significantly more patients in the treatment groups received steroids during the study follow-up compared with the “neither-treatment” group. Given the evidence which has emerged on the efficacy of dexamethasone in mortality reduction in COVID-19, the difference in steroid-use between groups may have biased the results in favour of treatment.

18. Sbidian et al — Non-peer-reviewed retrospective cohort study,19/06/20

A retrospective cohort study assessed the clinical effectiveness of oral HCQ in preventing death or allowing to 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.

19. Ip et al — Peer-reviewed retrospective cohort study, 13/08/20

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(77). 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%).

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 (61). 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.

21. Rosenberg et al — Peer-reviewed, retrospective cohort study, 11/05/20

A retrospective cohort study across 25 hospitals in New York State included a random sample of all admitted patients with laboratory-confirmed COVID-19 (52). 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.

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) (52).

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.

22. Carlucci et al Non-peer-reviewed retrospective cohort study, 08/05/20

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) (78). 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 (78).

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.

23. Geleris et al Peer-reviewed, retrospective cohort study, 07/05/20

An observational study in a New York hospital studied the association between hydroxychloroquine use and intubation or death (51). 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 (51).

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.

24. Mallat et al Peer-reviewed retrospective cohort study, 24/12/20

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) (79). 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.

25. Yu et al — Peer-reviewed retrospective cohort study, 15/05/20

A retrospective analysis of 550 critically ill patients with COVID-19, identified 48 patients who received hydroxychloroquine (oral 200mg twice daily for 7-10 days) and 502 patients who did not receive hydroxychloroquine (80, 81). 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, 62.5% were male. 99.1% of patients required oxygen therapy, while 63.5% 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%). Other antiviral drugs (lopinavir-ritonavir, entecavir hydrate, or ribavirin) were used concomitantly by 41.7% and 42.0% of patients in the HCQ and NHCQ groups, respectively. Interferon was used in none of the HCQ-treated patients, and 10.8% of the no-HCQ treated patients. Mortality was 47.4% (238/502) in the no-HCQ group and 18.8% (9/48) in the HCQ group (adjusted HR 0.36, 95% CI 0.16 to 0.61: p=0.006). 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<0.05). 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 (80, 81).

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. The groups appear to be somewhat well-balanced with some exceptions. 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.

26. Magagnoli et al — Peer-reviewed retrospective cohort study, 18/12/20

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 29, 2020, was conducted (82). Available data included inpatient, outpatient, laboratory and pharmacy claims data. Patients were treated with hydroxychloroquine alone (HC, n=198), hydroxychloroquine and azithromycin (HC/AZ, n=214) or no hydroxychloroquine (no HC=395).

The median age of the cohort was 68-71 years. Almost all patients included in the analysis were male (95.2%-97.0%). Baseline demographic characteristics were similar; however HC and HC/AZ were more likely to be prescribed to patients with elevated hepatic enzymes and inflammatory markers. There were 38 deaths (19.2%) in the HC group, 49 deaths (22.9%) in the HC/AZ group, and 37 deaths (9.4%) in the no HC group. The unadjusted rates of invasive mechanical ventilation were 16.7%, 19.1%, and 14.6% in the HC, HC/AZ, and no HC groups, respectively (p=0.37), in patients who were treated with HC prior to invasive mechanical ventilation. To account for differences in population characteristics, propensity scores for use of specific treatments were calculated based on clinical characteristics. Compared to the no HC group, there was a higher risk of death from any cause in the HC group (adjusted HR,

1.83; 95% CI, 1.16 to 2.89; P=0.009) but not in the HC/AZ group (adjusted HR, 1.31; 95% CI, 0.80 to 2.15; P=0.28). 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 almost exclusively to men, with a median age of 70 years. 23.0% of the No-HC group received azithromycin. Azithromycin has been suggested to have antiviral activity in its own right, though this is unproven (82).

27. Gautret et al — Peer-reviewed observational study report, 20/03/20

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 (64).

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. The clinical relevance of the chosen outcome is limited. 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. In a statement from the president of the International Society of Antimicrobial Chemotherapy (publisher of the journal which published this paper), the board of the society believes that the article does not meet the Society's expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety.

28. Million et al — Peer-reviewed case series, 05/05/20

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 (83, 84). 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 nine days of follow-up. Reasons for exclusion were provided for 350 patients, including 94 whose data was already published and 256 with to hydroxychloroquine and/or azithromycin, refusal or other reasons.

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 and no patient had QTc prolongation exceeding 500ms.

The findings of this study, regarding the efficacy of combination treatment, are difficult to interpret in the absence of a control arm (83).

29. Molina et al — Peer-reviewed case series, 28/03/20

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 (85).

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 (85). Repeated nasopharyngeal swabs were still positive for SARS-CoV2 RNA in 8/10 surviving patients at days 5 to 6 after treatment initiation (85).

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.

30. Gautret et al — Peer-reviewed case series 11/04/20

A second report by Gautret et al, expanded the initial case series of six patients treated with hydroxychloroquine-azithromycin to 80 patients (86). 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; 53.8% 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, one of whom died. 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 (86).

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

Key points:

RCTs have demonstrated no reduction in mortality with lopinavir-ritonavir in hospitalised patients with COVID-19, compared with standard of care. Full study reports of key clinical trials are awaited.

Summary of evidence:

Clinical evidence for the comparative efficacy of lopinavir-ritonavir for COVID-19 is available from six open-label RCTs, five of which failed to demonstrate a benefit for lopinavir-ritonavir versus standard-of-care, and one which did not include a standard-of-care control arm (14, 30, 87-90). The two largest of these studies, the WHO SOLIDARITY trial and the UK RECOVERY trial, have reported results showing no significant mortality benefit, and have stopped enrolling patients to the lopinavir-ritonavir arms of the studies (14, 91). Earlier RCTs reported no difference in time to clinical improvement or SARS-CoV-2 viral shedding, between lopinavir-ritonavir and standard of care (30, 88). Numerical differences in favour of lopinavir-ritonavir were observed in a number of secondary outcomes in one RCT, including a shorter stay in the intensive care unit, but these were not significant (88). 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, or those based on clinician decisions. A number of observational case reports have also been published (88, 92, 93).

Table 4: Source of clinical evidence for lopinavir-ritonavir in COVID-19

New additions to this version of the review are highlighted in yellow

Author (study name)	Study design	Peer-reviewed (Yes/no)	Publication date
1. Arabi et al	RCT	Yes	12/07/21
2. Pan et al (SOLIDARITY)	RCT	Yes	02/12/20
3. Horby et al (RECOVERY)	RCT	Yes	05/10/20
4. Li et al	RCT	Yes	04/05/20
5. Hung et al	RCT	Yes	08/05/20
6. Cao et al	RCT	Yes	18/03/20
7. Han et al	Case report	No	19/02/20
8. Lim et al	Case report	No	13/02/20

Background to lopinavir-ritonavir in COVID-19

From version 14 of this Review onwards, the literature search strategy for lopinavir-ritonavir will be restricted to peer-reviewed RCTs enrolling greater than 150 patients. Further details on this restriction to the search strategy can be found in Appendix 1.

Lopinavir-ritonavir is an antiretroviral fixed drug combination (HIV protease inhibitors), currently licensed in Ireland for the treatment of human immunodeficiency virus (HIV-1). (94) Lopinavir-ritonavir has been shown to have in vitro activity against SARS-CoV-1. (95-97). Limited clinical data has also been reported for lopinavir-ritonavir, combined with ribavirin and interferon alfa, in MERS (98). Lopinavir-ritonavir in combination with interferon-beta 1b is currently under investigation for the treatment of MERS-CoV (99). The potential for benefit from lopinavir-ritonavir treatment in COVID-19 has been well documented (100).

Clinical evidence

1. Arabi et al — Peer-reviewed RCT, 12/07/21

The REMAP-CAP trial is a large ongoing international adaptive platform clinical trial designed to determine the best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings (68). The part of REMAP-CAP reported in this paper was a placebo-control randomized open-label trial examining the impact of treatment with lopinavir-ritonavir, hydroxychloroquine, and combined therapy of lopinavir-ritonavir and hydroxychloroquine compared to no COVID-19 therapy in critically ill adult patients (≥18 years) with confirmed or suspected COVID-19 being treated in ICU with respiratory or cardiovascular organ failure support.

The primary endpoint was a composite ordinal scale of the number of organ support-free days (OSFD). Respiratory and cardiovascular organ support-free days were calculated up to day 32 with a 1.5-day difference considered to be the minimal clinically important difference and death assigned a score of -1.

726 patients were randomized to receive lopinavir-ritonavir (400mg lopinavir, 100mg ritonavir every 12hours for 5-14days) (n=268), hydroxychloroquine (2 loading doses of 800mg 6 hours apart, followed by 400mg every 12 hours for 12 doses) (n=52), combined therapy of lopinavir-ritonavir and hydroxychloroquine (n=29) or placebo (no COVID-19 anti-viral therapy) (n=377). The patients were mostly white (73%) and male (70%) with a mean age across the treatment groups of between 56-61 years. 99.4% of patients were receiving

respiratory support (high-flow nasal cannula, non-invasive or invasive ventilation or ECMO) and 19.8% were receiving vasopressor support.

The median organ support-fee days among patients were 4 (-1-15) in the lopinavir-ritonavir treatment group, 0 (-1 to 9) in hydroxychloroquine treatment group, and -1 (-1 to 7) in the combined therapy of lopinavir-ritonavir and hydroxychloroquine group compared with 6 (-1 to 16) in the placebo group. The corresponding median adjusted ORs were 0.73 (95% CI, 0.55 to 0.99) for the lopinavir-ritonavir treatment group, 0.57 (95% CI, 0.35 to 0.83) for the hydroxychloroquine treatment group, and 0.41 (95% CI, 0.24 to 0.72) for the combined therapy of lopinavir-ritonavir and hydroxychloroquine group when compared to placebo. All three interventions decreased hospital survival compared to control, with the corresponding median adjusted ORs of 0.65 (95% CI, 0.45 to 0.95), 0.56 (95% CI, 0.36 to 0.89) and 0.36 (95% CI, 0.17 to 0.73) respectively, yielding high probabilities of harm (98.5%, 99.4% and 99.8% respectively). Serious adverse events were reported in 5.1% of patients randomized to receive lopinavir-ritonavir, 6% to receive hydroxychloroquine, 3.7% to receive combined therapy of lopinavir-ritonavir and hydroxychloroquine and 3.3% in the control arm.

The REMAP-CAP is a well conducted trial, designed to demonstrate robust clinically meaningful outcomes. However, the open-label nature of the trial is a limitation although it was mitigated somewhat by neither clinical staff nor the trial steering committee having access to aggregate patient outcomes. Enrolment in the hydroxychloroquine and combination therapy arms was halted on July 13, 2020 based on published concerns regarding the safety and efficacy of hydroxychloroquine. Enrolment into the lopinavir-ritonavir arm was halted on November 19, 2020, after reaching the pre-specified futility threshold.

2. Pan et al (WHO SOLIDARITY – interim results) Peer-reviewed RCT, 02/12/20

Full details of this study are discussed in the "Evidence for Clinical Efficacy of Remdesivir" section of this review. In summary, in a simple, international, multi-centre, adaptive, randomised, open-label, controlled clinical trial launched by the World Health Organization (WHO) and partners, evaluating the clinical efficacy and safety of four treatment options against standard of care for COVID-19 in hospitalised patients, no study drug had any definite effect on mortality, either overall or in any subgroup defined by age or ventilation at entry (14). Death rate ratios were remdesivir RR=0.95, 95% CI 0.81 to 1.11, p=0.50; hydroxychloroquine RR=1.19, 95% CI 0.89 to 1.59, p=0.23; lopinavir RR=1.00, 95% CI 0.79 to 1.25, p=0.97 and interferon RR=1.16, 95% CI 0.96 to 1.39, p=0.11. No study drug appreciably reduced initiation of ventilation in those not already ventilated. Analysis of the proportions hospitalised at day 7 showed that treatments scheduled to last >7 days increased the percentages of patients on those treatments remaining in hospital (as expected in an open-label trial), but the lack of differences in the increases across the treatments indicated no

appreciable effect in reducing time to recovery. The lopinavir-ritonavir arm of the study was discontinued for futility on July 4 2020 (14).

3. Horby et al (RECOVERY) Peer-reviewed RCT, 05/10/20

Full details of this study are discussed in the "Evidence for Clinical Efficacy of hydroxychloroquine" section of this review. In summary, RECOVERY is a randomised, open-label trial investigating whether various treatments are beneficial for people hospitalised with suspected or confirmed COVID-19. Hospitalised patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection were randomised in a ratio of 2:1 to either usual standard of care or usual standard of care plus lopinavir-ritonavir (400mg/100mg orally every 12 hours for 10 days or until discharge) 800mg at zero and 6 hours, followed by 400mg twice daily, starting at 12 hours, for the next 9 days or until discharge) or one of the other available treatment arms. The primary outcome was all-cause mortality, assessed after 28 days, with further planned analysis at 6 months. Enrolment of participants to the lopinavir-ritonavir arm was closed on 29th June 2020 following a review of data by the chief investigators and steering committee.

While the lopinavir-ritonavir arm of the study was open, 1,616 patients were randomized to lopinavir-ritonavir and 3,424 patients to usual care alone (91). Baseline demographics and disease characteristics were well-balanced across treatment groups. The mean age of the cohort was 66.2 years and 19%-20% were female. 38%-40% of patients were receiving mechanical ventilation at randomisation, while 25% were receiving oxygen only. Use of azithromycin or other macrolide, and dexamethasone was similar between study arms. The mean time since symptom onset was 8 days. 87%-88% of patients had laboratory confirmed SARS-CoV-2 infection. At least one major co-morbidity was present in 57% of the cohort. There was no significant difference in the primary endpoint of 28-day mortality (23% lopinavir-ritonavir vs 22% usual care; RR 1.03, 95% CI 0.91 to 1.17; p=0.60). The results were similar across pre-specified subgroups including those who tested positive for SARS-CoV-2. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay.

RECOVERY is a well-designed study and has reported robust findings on the efficacy of hydroxychloroquine in the enrolled population of hospitalised patients. The fatality rate in the usual care arm is reported as being consistent with hospitalised patient cohorts across the UK and elsewhere. The secondary outcomes of the study, time until discharge and the composite endpoint of initiation of mechanical ventilation or death, could have been influenced by the study's open-label design as management strategies impacting these outcomes are at the discretion of the investigator, who was aware of treatment assignment. The findings cannot be extrapolated to patients with less severe COVID-19.

4. Li et al

Peer-reviewed RCT, 04/05/20

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) (30). A peer-reviewed version of the manuscript was published on 4th May 2020. 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 (101). 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 mean age of the cohort was 49.4 years 41.2%-50% were male. 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). There were also differences in the use of glucocorticoids across treatment groups (5.7%-20.6%). 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 (30). The imbalance in the use of glucocorticoids may have affected results across treatment groups given the efficacy observed with this treatment in other trials.

5. Hung et al

Peer-reviewed RCT, 08/05/20

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.

6. Cao et al

Peer-reviewed RCT, 18/03/20

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 (88). 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 (98) .

7. Han et al — Case report, 19/02/20

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 (92). 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 (92).

8. Lim et al

Case report, 13/02/20

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 (93). 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 (93). 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 (94).

International clinical trials of investigational antiviral treatments for COVID-19

Researchers have registered hundreds of clinical trials for COVID-19, many of which are actively recruiting. COVID-19 trials need to be well designed and adequately powered to generate robust evidence (102). 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 treatment of 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) (103). 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 (103). To date, over 300 study locations across 21 countries have participated in the study, randomising patients with suspected or proven COVID-19, including three Irish hospitals: Beaumont Hospital, St. Vincent's University Hospital and University Hospital Galway (76). 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. Randomisation was initially 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, lopinavir-ritonavir and

more recently ivermectin; Immunomodulation was amended to include interferon-beta 1a, anakinra (interleukin-1 receptor antagonist), and interleukin-6 receptor antagonists tocilizumab and sarilumab; the corticosteroid domain was modified to include a higher dose. Other domains have since been added or are under construction e.g. Immunoglobulin domain, Therapeutic anticoagulation domain and Vitamin C domain. 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 (103). On 2 September 2020, REMAP-CAP investigators published results of the corticosteroid domain of the study, finding that among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early following publication of the UK RECOVERY trial results and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions (103). On 11 January 2021, the REMAP-CAP trial announced that recruitment had been halted into its convalescent plasma arm following interim analysis that found that the probability of benefit was 2.2%.

World Health Organisation SOLIDARITY

The Solidarity trial is a simple, 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) (78, 79, 81, 104). It is one of the largest international randomised trials for COVID-19 treatments, and has enrolled over 14,000 patients in 600 hospital sites in over 50 countries. Ireland's participation in the trial was announced on 26/06/20. The trial procedures are minimal but rigorous; to allow the involvement of hundreds of potentially over-stretched hospitals. The primary objective is to assess effects on in-hospital mortality (i.e., mortality during the original episode of hospitalisation; follow-up ceased at discharge) in all patients and also in those with moderate COVID and in those with severe COVID (subsequently defined as ventilated when randomised). Secondary outcomes included initiation of ventilation and hospitalisation duration. Add-ons to the Solidarity trial include the Canadian CATCO study and the European Discovery trial, which both record additional outcomes. 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. Interim results (discussed above, under Pan et al) concluded that remdesivir, hydroxychloroquine, lopinavir-ritonavir and IFN β regimens appeared to have little or no effect on hospitalised COVID-19(14). Hydroxychloroquine, lopinavir-ritonavir and IFN β were discontinued for futility on June 18. July 4, 2020 and October 16 2020, respectively (14).

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, and is an add-on to the SOLIDARITY trial (EU 2020-000936-23) (103). It is a phase 3, open-label, randomised, adaptive, controlled trial analysing the safety and efficacy of four investigational therapies in participants hospitalised with COVID-19 across France, Belgium, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK (105). The primary endpoint is subject clinical status (on a 7-point ordinal scale) at day 15 (103). In line with the SOLIDARITY trial investigators, enrolment into the hydroxychloroquine, lopinavir-ritonavir and IFN β groups of the Discovery trial was stopped prematurely. As an add-on to the SOLIDARITY trial, the Discovery trial provides more detailed data on safety and clinical and laboratory surrogates, in particular virological data. A non-peer-reviewed preprint of results from the lopinavir-ritonavir, lopinavir-ritonavir+interferon beta-1a, and hydroxychloroquine arms of the study was published in January 2021, confirming the results of the SOLIDARITY trial and additionally reporting no SARS-CoV-2 RNA clearance in respiratory tract specimens by studied drugs (106).

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 (103). 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 (79). 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. Enrolment into to the hydroxychloroquine and lopinavir-ritonavir arms of the trial has been stopped due to lack of efficacy, as discussed in the relevant sections above (107) (87). As of January 2021, the RECOVERY trial is recruiting patients into the following arms: low dose

dexamethasone (children only), colchicine, tocilizumab, aspirin and REGN-COV2 (a combination of monoclonal antibodies directed against coronavirus).

United States: ACTT and Orchid trials

A number of 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, was 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 was a multicentre, double-blind, placebo-controlled, randomised clinical trial evaluating hydroxychloroquine for the treatment of adults hospitalised with COVID-19 (NCT04332991) (108). The primary outcome was 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. Further details of study results are provided in the Evidence for the clinical efficacy of hydroxychloroquine section of this report. 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) (76). 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 (76). Results from the ACTT trial showed some benefit from remdesivir compared with placebo. The final report of the study is described in the remdesivir section of this review (15). The next iteration of the ACTT trial, ACTT2, examined if adding baricitinib, a JAK inhibitor licensed for the treatment of rheumatoid arthritis, provided additional benefit when added to remdesivir The ACTT2 trial does not include a placebo arm (109). The A5395 study aimed to evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalisation or death in symptomatic adult outpatients with COVID-19. The study was closed following enrolment of just 20 participants, as it was considered by the investigators to be highly unlikely that the study would be able to enrol to completion and meet its intended objectives (110).

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.

Sofosbuvir and daclatasvir (with or without ribavirin)

Three comparative studies, investigating the efficacy of sofosbuvir and daclatasivir (with or without ribavirin) compared with standard of care, were conducted in Iran and published on 19/08/20 in the same journal (111-113). All studies investigated duration of hospital stay as the primary endpoint. In all studies, patients received lopinavir-ritonavir and hydroxychloroquine in addition to the trial-allocated treatment, in accordance with national guidelines. Two trials reported inconsistent findings, with the combination of sofosbuvir/daclatasvir/ribavirin showing no difference in duration of hospital stay compared with standard of care in one trial, and the combination of sofosbuvir/daclatasvir showing a significant reduction in duration of hospital stay compared with standard of care in the other trial (111, 113). A third, observational study reported a significant reduction in duration of hospital with sofosbuvir/daclatasvir treatment compared with ribavirin alone (112). In this study, subjects were allocated to study arms based on which specialist was on-call at the time of their admission. The studies contained small patient numbers (n=48, n=62, n=66), which led to an imbalance in baseline characteristics in the case of the two RCTs. The method of allocation in the observational study may introduce bias, particularly as no information on standard of care was provided.

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 (114). 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 (115, 116). 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 (20). 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 (117). 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 (114). 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 (118).

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) (119). Eligible patients had demonstrated respiratory symptoms and imaging-confirmed pneumonia. After 4 to 12 days' treatment, all eleven patients enrolled were discharged from hospital (103). The ERG is not aware that danoprevir is readily available for use in Ireland.

Other treatments with possible anti-viral activity

Interferons

Interferon-alpha (IFN α) and interferon-beta (IFN β) 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. IFN β 1a and IFN β 1b are licensed in Ireland for the treatment of multiple sclerosis. IFN α 2b is licensed in Ireland for the treatment of chronic hepatitis B and C and various haematological malignancies. Both IFN α and IFN β have shown effective in vitro inhibition of SARS-CoV-1 replication, with IFN β showing the greatest potency (120). Clinical improvements have been observed in vivo with IFN β -beta in MERS-CoV (121). The combination of IFN α 1b with lopinavir-ritonavir led to lower mortality than placebo among patients who had been hospitalised with laboratory-confirmed MERS in the MIRACLE study in Saudi Arabia (122). A randomised, double-blind, placebo-controlled trial of IFN α -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 (123).

Positive results have emerged from a phase II double-blind placebo-controlled trial (Clinicaltrials.gov NCT 04385095, EudraCT: 2020-001023-14) of nebulised IFN β-1a in hospitalised COVID-19 based on the WHO ordinal scale for clinical improvement (odds of

improvement, OR 2.32; p=0.033) (124). Studies investigating the use of IFN β in COVID-19 have emerged, including the WHO-SOLIDARITY trial (described earlier in this report, under Pan et al), an RCT of IFN β-1a and an RCT of IFN β-1b compared with standard of care in patients with severe COVID-19) (14, 125, 126). The WHO study found that IFN β (mainly subcutaneous) provided no benefit and has dropped the treatment arm from the study (14). The other RCTs also included subcutaneous IFN were both were conducted with small sample sizes (N=81, N=66) and reported inconsistent results for the primary endpoint of time to clinical improvement on a six-category ordinal scale, ranging from death to discharge. Both studies identified an improvement in the discharge rate at day 14. It is unlikely that either of these studies were adequately powered to detect significant differences in clinical outcomes. Their open-label design also is problematic in the assessment of outcomes relating to discharge etc, as discussed elsewhere in this review. 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 (20).

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 (103). 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, and inflammatory markers were reported (127). No adverse effects were judged to be meplazumab-related. 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 (128). 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 (129). 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 (129). 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 (130). 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 (20).

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 and US were searched for evidence of ongoing or completed clinical trials.

The following amendments to the search strategy apply:

Version 15 - current:

- **The literature search strategy for remdesivir will restrict the inclusion of observational studies to those which include ≥ 100 participants treated with remdesivir.** This restriction is due to the growing evidence base of large and informative studies and the significant potential for bias from small, observational studies of treatments for COVID-19.

Version 14 – current:

- **The literature search strategy for hydroxychloroquine and lopinavir-ritonavir will be restricted to peer-reviewed RCTs enrolling greater than 150 patients.** This restriction is due to the growing evidence base of large, informative RCTs and meta-analyses of hydroxychloroquine, and the significant potential for bias from small, observational and non-peer-reviewed studies of treatments for COVID-19. The reliability of many observational studies is limited by the use of inappropriate statistical methodology, required to minimise the potential for bias and confounding associated with non-random treatment allocation. 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 peer-reviews isn't necessarily a guarantee of robust clinical trial design and reporting, it is considered by the Review Group to be an appropriate limit for the hydroxychloroquine search strategy, given the volume of poor-quality studies that continue to emerge.

Search strategy 20th January 2021

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)

The WHO Living Guideline on Therapeutics and COVID-19 (06 July 2021) makes the following recommendations with regard to antiviral agents:

- We recommend against administering hydroxychloroquine or chloroquine, or lopinavir-ritonavir for treatment of COVID-19. This recommendation applies to patients with any disease severity and any duration of symptoms.
- We suggest against administering remdesivir in addition to usual care(5).

European Medicines Agency (EMA)

The EMA granted conditional marketing authorisation to remdesivir (Veklury®) on 03rd July 2020, for the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. In relation to hydroxychloroquine and chloroquine, the EMA has stated that these medicines have not shown any beneficial effects in treating COVID-19 in large RCTs, citing the SOLIDARITY and RECOVERY trials. Earlier recommendations included:

- 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 (29th May 2021).
- 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 (29th May 2021).
- 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 (116, 131).

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