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Position Statement: Management of COVID-19 in adults with investigational agents

Interim Support for clinicians in England

Document management

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File name:	CTAG/PS/COVID19/Interimsupport
Version number:	2.0
Available on:	https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/0_covid19_interim_position_statement.pdf
Disseminated to:	Infectious Diseases, Virology, Drugs & Therapeutics Committees and Pharmacy teams
Publication date:	01 April 2020
Review date:	This document is subject to constant review. If you identify any outdated information, please contact admin.ncl-mon@nhs.uk .

Document control

Date	Version	Amendments
23 Mar 2020	1.0	New document
23 Mar 2020	1.1	Updated Gilead compassionate use scheme eligibility criteria
27 Mar 2020	1.2	Added NHS England and NHS Improvement speciality guide for patient management; added MHRA advice on chloroquine and hydroxychloroquine; added hydroxychloroquine arm of RECOVERY study; added link to NIHR website.
01 Apr 2020	2.0	Updated evidence summaries in Appendix 1 (new trials for lopinavir/ritonavir and chloroquine). Merged 'Position statement' and 'Decision Support Tool' into a single document. Updated Section 3 with new trials. Updated Figure 1 with relationship between RECOVERY and PRINCIPLE/REMAP-CAP.

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1. Aim

- 1.1. This position statement provides interim supporting information on the pharmacological management of adult patients with COVID-19 and will be superseded when specific guidance is published by NHS England, Department of Health and Social Care or Public Health England.
- 1.2. Information contained within this position statement does not represent a 'recommendation', however it is intended to provide support to healthcare professionals when considering available treatment options.

2. Interim supporting information

- 2.1. There are no anti-viral medicines or vaccinations approved to treat or prevent human coronaviruses.¹ There is no randomised controlled trial evidence that any treatment beyond best supportive care delivers improved outcomes for patients with COVID-19 as of 31 March 2020.^{2,3}

Several investigative agents have potential to be repurposed for the management of COVID-19^{1,2}; the risk-benefit of these agents is summarised in

- 2.2. Appendix 1.
- 2.3. Investigative agents should only be used in the context of a clinical trial using supplies allocated for clinical trial use^a.
- 2.4. As relevant trials open, hospitals managing COVID-19 cases are encouraged to engage with their R&D services to adopt trials of investigative agents and establish capacity to recruit into those trials – refer to Section 3.
 - The [RECOVERY](#) trial (UK study) is endorsed by NHS England^b and opened to recruitment at all Trusts on 20 March 2020
 - Standard of care [SoC] *versus* lopinavir/ritonavir + SoC *versus* hydroxychloroquine + SoC *versus* interferon beta-1a + SoC *versus* dexamethasone + SoC
 - The [REMAP-CAP](#) trial (international critical care study, UK sites) is also recruiting. Two new [domains](#) specific for COVID-19 have been granted ethical approval:
 - Antiviral therapy: evaluating no antiviral therapy (and no placebo), and lopinavir/ritonavir
 - Immune modulation therapy: evaluating no immune-modulating therapy (and no placebo), interferon-beta-1a, and anakinra
- 2.5. For clinicians unable [to](#) access investigative agents within the context of a clinical trial, remdesivir can be considered for patients who meet the Gilead compassionate access programme eligibility criteria – refer to Section 4. This scheme is due to be replaced by an expanded access programme in the near future⁵.
- 2.6. Clinicians should be reassured that, irrespective of whether or not their patients meet compassionate access criteria, best supportive care remains the optimal approach to management outside of a clinical trial.
- 2.7. Recruitment into the ISARIC-CCP study is strongly encouraged for any patient, including those receiving experimental or unlicensed therapies. Co-recruitment into the ISARIC-CCP study does not preclude enrolment into a clinical trial of investigative medicinal products (CTIMP).
- 2.8. Patients may be admitted into hospitals receiving interventional treatment from primary care e.g. PRINCIPLE trial. Where identified, treatment should usually be continued if clinically appropriate as enrolment into subsequent interventional trials may not be precluded (Figure 1).
- 2.9. No recommendations can be made at the current time about the appropriate use of off-label immunomodulatory medicines for the treatment of coronavirus outside of a clinical trial e.g. anakinra, tocilizumab, sarilumab or ruxolitinib.

^a [MHRA](#) recommends chloroquine and hydroxychloroquine are only used for the treatment and prevention of COVID-19 within the context of a clinical trial⁴

^b [NHS England & NHS Improvement](#) suggest Trusts consider enrolling patients into UK clinical trials, including the RECOVERY trial³

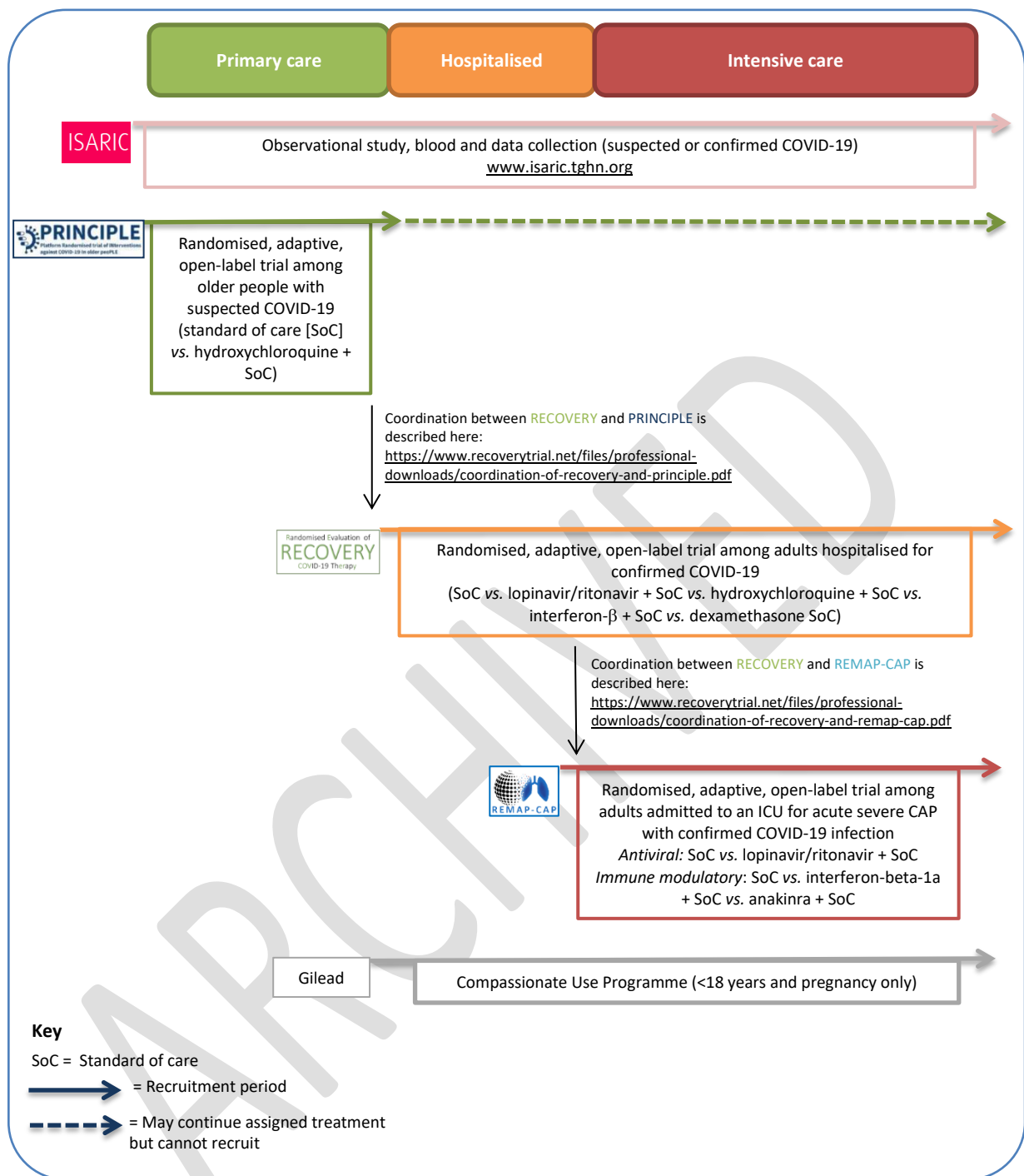


Figure 1: Active UK Clinical Studies as at 30 March 2020 (Figure will be updated as new studies are activated for UK patient recruitment). Participation for COVID-19 trials will be through adoption at local sites, information should be available at through local Research and Development Offices. There are a number of trials that are also undergoing contract amendments to include patient recruitment due to complications of COVID-19, including HLH and ARDS that your patients may be eligible for.

3. UK clinical studies

- 3.1. NIHR is working with the Department of Health and Social Care (DHSC) to coordinate the national research agenda⁶.
- 3.2. Organisations should prioritise support for studies which have been nationally prioritised and pause any local studies that impede their ability to contribute to national research efforts⁶.
- 3.3. A complete list of nationally prioritised research studies for COVID-19 is available on the [NIHR website](#)

- 3.4. The following interventional clinical trials and national observational studies are active in the UK for recruitment:
- ISARIC-CCP UK [Case Record Forms \(CRF\)](#) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19
 - [PRINCIPLE](#) trial (UK study open to Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) general practices) for patients with possible COVID-19 if ≥ 65 years or ≥ 50 years with pre-existing comorbidities
 - Standard of care [SoC] *versus* hydroxychloroquine + SoC
 - [RECOVERY](#) trial (UK study open to all Trusts)
 - Standard of care [SoC] *versus* lopinavir/ritonavir + SoC *versus* hydroxychloroquine + SoC *versus* interferon beta-1a + SoC *versus* dexamethasone + SoC
 - [REMAP-CAP](#) (international critical care study, UK sites); expanded to include two new [domains](#) specific for COVID-19 have been granted ethical approval:
 - Antiviral therapy: evaluating no antiviral therapy (and no placebo), and lopinavir/ritonavir
 - Immune modulation therapy: evaluating no immune-modulating therapy (and no placebo), interferon-beta-1a, and interleukin-1 receptor antagonist (anakinra)
- 3.5. The following interventional clinical trials and national observational studies are emerging or proposed in the UK:
- GS-5773 trial in patients with severe infection (multinational study, limited UK sites)
 - Part A (not mechanically ventilated): Remdesivir 5 days + SoC *versus* Remdesivir 10 days + SoC
 - Part B (mechanically ventilated and extension treatment group): Remdesivir 10 days + SoC
 - GS-5774 trial in patients with moderate infection (multinational study, limited UK sites)
 - Part A: SoC *versus* Remdesivir 5 days + SoC *versus* Remdesivir 10 days + SoC
 - Part B (extension treatment group): Remdesivir 10 days + SoC
 - Study to evaluate tocilizumab in patients with severe COVID-19 Pneumonia (tocilizumab *versus* placebo)
 - DISCOVERY trial (WHO pan-European; SoC *versus* remdesivir + SoC *versus* lopinavir/ritonavir + SoC *versus* lopinavir/ritonavir + interferon beta-1a injection + SoC)
 - ACTT trial (limited UK sites; remdesivir *versus* standard-of-care)
 - Proposal to amend the [REALIST](#) trial (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab

4. Gilead compassionate use programme

Remdesivir infusion (formerly GS-5734; unlicensed medicine)						
Eligibility criteria*	Exclusion criteria*	Dose	Duration	Special precautions	Drug specific monitoring	Supply route*
Pregnant women or children less than 18 years of age with severe manifestations of the disease ⁵	Nil pre-specified.	<p>Adult and adolescent (≥ 40 kg) - 200 mg IV loading dose on Day 1 followed by 100 mg IV once-daily on Day 2 onwards.</p> <p>Infuse dose over 30 minutes⁷</p> <p>Dosing information may vary to the above and should be guided by ID/Virology and dosing protocol provided by Gilead.</p>	10 days but may continue for an additional 4 days at 100 mg IV once-daily if COVID-19 remains detectable at day 10 of treatment. ⁷	No information for dose adjustment in liver and renal impairment (likely would be excluded from the programme)	<p>Limited information available, generally well tolerated.</p> <p>Reversible Grade 1 or 2 ALT or AST elevation observed.⁴</p> <p>Daily monitoring of renal (creatinine and BUN) and liver (ALT, AST) functions should be performed⁷</p>	<p>Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/.</p> <p>Any communication with Gilead should include UKICOVID-19@gilead.com³</p>
<p>Further information: https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1</p> <p><i>*As at 22 March 2020 Gilead is transitioning the provision of emergency access to remdesivir from individual compassionate use (CU) to expanded access programs (EAP). During this transition period Gilead is unable to accept new individual CU requests however anticipate the EAP will initiate in a similar timeframe that any new requests for CU would have been processed. Exceptions will be made only for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.</i></p>						

5. References

1. Li, G. & De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* **19**, 149–150 (2020).
2. UK Airborne High Consequence Infectious Diseases Network. Treatment of COVID-19 with investigational antiviral agents: Interim Decision Support Tool for clinicians. (2020).
3. NHS England & NHS Improvement. Clinical management of persons admitted to hospital with suspected COVID-19 infection v1. <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/clinical-management-of-persons-admitted-to-hospita-v1-19-march-2020.pdf> (2020).
4. MHRA. Chloroquine and Hydroxychloroquine not licensed for coronavirus (COVID-19) treatment. <https://www.gov.uk/government/news/chloroquine-and-hydroxychloroquine-not-licensed-for-coronavirus-covid-19-treatment>.
5. Email communication with Gilead (Dr Shayon Shalehi). (2020).
6. National Institute for Health Research. NIHR's response to COVID-19. <https://www.nihr.ac.uk/covid-19/>.
7. World Health Organisation. WHO R&D Blueprint – Ad-hoc Expert Consultation on clinical trials for Ebola Therapeutics. Appendix 4. Summaries of evidence from selected experimental therapeutics. (2018).

6. Provenance: COVID-19 Therapeutics Advice & Support Group (CTAG)

The UK collaborative COVID-19 Therapeutics Advice & Support Group comprises of the following:

- Dr Jake Dunning (Consultant, Infectious Diseases; Royal Free London)
- Dr Sir Michael Jacobs (Consultant, Infectious Diseases; Royal Free London)
- Dr Michael Brown (Consultant, Infectious Diseases; UCL Hospitals)
- Prof Graham Cooke (Consultant, Infectious Diseases; Imperial)
- Dr Jonathan Edgeworth (Consultant, Microbiology; Guys & St Thomas')
- Prof Thomas Harrison (Consultant, Infectious Diseases; St Georges)
- Dr Laurence John (Consultant, Infectious Diseases; London North West)
- Prof Mahdad Noursadeghi (Consultant, Infectious Diseases; UCL Hospitals)
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- Dr Anna Tunbridge (Consultant, Infectious Diseases; Sheffield)
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- Dr Meera Chand (Consultant, Microbiology; Public Health England)
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- Dr Yusri Taha (Consultant, Virology; Newcastle)
- Dr Katrina Pollock (Consultant, Virology; Imperial)
- Dr Lance Turtle (Consultant, Infectious Diseases, Liverpool)
- Mr Paul Wade (Consultant Pharmacist, Infectious Diseases; Guys & St Thomas')
- Dr Reecha Sofat (Consultant Clinical Pharmacologist and NCL Joint Formulary Committee Chair; UCLH)
- Dr Pritesh Bodalia (Pharmacist, UCL Hospitals)
- Mr Andrew Barron (Pharmacist, North Central London)
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Appendix 1: Evidence base for investigational antiviral agents to treat COVID-19

Disclaimer


Due to the urgency for interim guidance, only a limited number of agents have been assessed and a wholly systematic approach to assessing the evidence (such as GRADE) has not been performed. Some subjective judgments are solely the consensus opinion of the authors and consulted experts.

The focus here is on investigational antiviral treatments for managing hospitalised COVID-19 patients. Supportive care and treatment of co-infections and complications, such as ARDS, are not addressed: generic guidance is [available elsewhere](#) and is recommended for use until specific evidence emerges relating to COVID-19.

Methods

COVID-19 is caused by infection with the newly emerged betacoronavirus SARS-CoV-2.

We reviewed the available data on treatment of betacoronaviruses and broadly hierarchised the evidence according to the following matrix:

Virus tested	Evidence of benefit	
SARS-CoV-2	Human controlled intervention trial	Greatest evidence  Least evidence
SARS-CoV	Human observational study	
MERS-CoV	Nonhuman primate experimental	
Other betacoronavirus	Small animal experimental	
	In vitro	
	Theoretical	

For relevant compounds, we then also considered the available safety data.

Therapies that are plausible and supported by reasonable body of *in vitro*, animal and/or clinical data are shown in the following tables. A large number of other compounds have been evaluated for *in vitro* inhibition of SARS-CoV-2 and/or other betacoronavirus replication, and some have demonstrated an inhibitory effect at serum concentrations that might be achieved in patients. However, without animal studies or well-documented experience of clinical use in comparable contexts, these are not currently recommended for clinical use in COVID-19 patients. Similarly, some drugs have theoretical potential for benefit in COVID-19 patients but no supporting data, and are not recommended for use. Drugs in these categories are not listed in the tables, with the exception of any that have been widely proposed as current treatment options for COVID-19.

Evidence summary

The therapies are divided into two categories in the following tables based on current evidence:

- 1) Benefit may exceed risk, potentially suitable for compassionate use (Table 1)
- 2) Inadequate data to recommended compassionate use currently, await further data (

4) Table 2)

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Table 1: Evidence base for specific therapies for SARS-CoV-2 infection: Benefit may exceed risk, potentially suitable for compassionate use

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical

Remdesivir

Studies performed*	Data: SARS, MERS and other	Data: SARS-CoV-2	Safety profile	UK feasibility
<p>Siv; Miv; S2iv Sa; Ma</p> <p>Several non-UK S2c studies in progress and expected to report Apr 2020</p>	<p>Nucleotide prodrug with activity against a number of unrelated RNA viruses. Potent inhibition of SARS-CoV, MERS-CoV and bat coronaviruses with pandemic potential in human airway epithelial cells <i>in vitro</i>, with sub-micromolar EC50 values. In a mouse model of SARS-CoV, prophylactic and early therapeutic administration significantly reduces lung viral load and improves clinical signs of disease and respiratory function; later treatment, initiated at peak viral replication, reduces lung viral loads but does not alter clinical outcome. In a nonhuman primate model of MERS-CoV infection, prophylactic or early treatment improves clinical respiratory function and radiological signs, and reduces lung viral load and histopathological changes. Direct comparison with combination lopinavir/ritonavir and interferon-beta <i>in vitro</i> and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.</p>	<p>Inhibits SARS-CoV-2 replication in Vero cells with a low micromolar EC50 value.</p>	<p>Manufacturer reports two phase 1 human trials completed, results not published. Phase 2 trial in Ebola Virus Disease (EVD) survivors (NCT 02818582) fully recruited but not yet reported. Extensive therapeutic use in 2018-20 Ebola outbreak in DRC, but trials designed for efficacy and only limited interpretation of safety is possible: no significant adverse safety signal detected.</p>	<p>Limited supply available for compassionate use (March 2020) and use is restricted to specific patient groups; refer to compassionate use programme details at: https://rdcvu.gilead.com</p> <p>International clinical trials (manufacturer's website): https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials</p>

Table 2. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommended compassionate use currently, await further data

*S=SARS, M=MERS, S2=SARS-CoV-2; iv=in vitro, a=animal, c=clinical

Lopinavir/ritonavir

Studies performed*	Data: SARS, MERS and other	Data: SARS-CoV-2	Safety profile	UK feasibility
Siv; Miv Ma Sc; S2c	<p>Protease inhibitor developed for HIV, a completely unrelated virus. In vitro data for both MERS and SARS-CoV are variable but suggest low potency inhibition at clinically achievable concentrations. No animal studies of SARS-CoV. In a nonhuman primate model of MERS, early treatment improved clinical, radiological and pathological features and reduced viral loads. In two retrospective, matched cohort studies of SARS, early but not rescue LPV/r treatment was associated with improved clinical outcomes, but interpretation is difficult because of multiple other uncontrolled interventions (ribavirin, corticosteroids) in these patients. Compassionate use in the S. Korea MERS outbreak was not informative about efficacy; no preliminary results available from ongoing MERS clinical trial in KSA. Combination LPV/r and ribavirin appeared beneficial in a small study of post-exposure prophylaxis against MERS in healthcare workers.</p> <p>Direct comparison between remdesivir, lopinavir/ritonavir, and interferon-beta <i>in vitro</i> and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.</p>	<p>Unpublished data indicate that lopinavir is inhibitory at uM concentrations for SARS-CoV-2 in Vero cell culture.. One observational study in COVID-19 patients did not find reduced duration of viral RNA detection in those receiving lopinavir-ritonavir.</p> <p>An open-label RCT of hospitalised adults in China with severe COVID-19 (n=199) found no benefit in time to clinical improvement for lopinavir-ritonavir over standard care. Lopinavir-ritonavir recipients spent less time in hospital (12 vs. 14 days) and less time in intensive care (6 vs. 11 days).</p>	<p>Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common.</p> <p>Note multiple significant drug-drug interactions.</p>	<p>Licensed for the treatment of HIV-1 infection.</p> <p>Included as an arm in the UK RECOVERY trial and REMAP-CAP trial (recruiting).</p>

Chloroquine (CQ) / Hydroxychloroquine (HCQ)

Studies performed*	Data: SARS, MERS and other	Data: SARS-CoV-2	Safety profile	UK feasibility
Siv; S2iv; S2c	Inhibitory <i>in vitro</i> for SARS-CoV but the selective index is low. In one murine model of SARS intraperitoneal chloroquine was ineffective in inhibiting lung virus titers. For multiple other viruses, potent <i>in vitro</i> activity has not translated into benefit in animal or clinical studies. In some cases, CQ has been shown to enhance viral replication in animal models, probably because of its immunomodulatory effects. In both a nonhuman primate model and clinical trial in chikungunya infection (which is unrelated to SARS-CoV-2), CQ treatment resulted in worse outcomes, despite promising antiviral activity <i>in vitro</i> .	<p>Effective inhibition of SARS-CoV-2 replication <i>in vitro</i>.</p> <p>HCQ given in a small (n=36), open-label, non-randomised trial in France, with and without azithromycin, with a reduction in viral load reported; however, no quantitative PCR results, 6 patients were excluded, no ITT analysis, and trial was underpowered.</p> <p>Abstract from China reported small (n=30) randomised trial of HCQ, with no difference observed in negative conversion rate of SARS-CoV-2 PCR at day 7 between HCQ group and standard care group.</p>	Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and studies, albeit with unrelated viruses, raise concerns (see data).	<p>Various licensed indications, including malaria and rheumatoid arthritis.</p> <p>Included as an arm in the UK RECOVERY trial and PRINCIPLE trial (recruiting).</p>

Interferon (systemic)

Studies performed*	Data: SARS, MERS and other	Data: SARS-CoV-2	Safety profile	UK feasibility
<p>Siv; Miv Sa; Ma Sc; Mc</p>	<p>Type I (α, β), type II (γ), and type III (λ) IFNs all show activity against SARS-CoV in extensive <i>in vitro</i> studies. Type I (α, β) IFNs have shown activity in limited animal and observational clinical studies. Dose-related reductions in lung viral titers were found in In mice dosed intraperitoneally with IFN-B/D beginning 4 h after SARS-CoV exposure. One small observational study of IFN-aflacon-1 combined with corticosteroids reported improved clinical outcomes in SARS.</p> <p><i>In vitro</i>, MERS-CoV appears to be more sensitive to type I IFNs than SARS-CoV, especially IFN-β. Some animal evidence of benefit of early treatment with IFN-β1b in nonhuman primate model of severe disease. Observational studies of IFN-α combined with ribavirin have yielded inconclusive results; the largest study found no evidence for reduced mortality or for an antiviral effect. There are no preliminary results available from ongoing MERS clinical trial of systemic IFN- β-1b combined with lopinavir-ritonavir in the Kingdom of Saudi Arabia.</p>	<p>Unpublished <i>in vitro</i> data indicate that SARS-CoV is more susceptible to IFN-β-1a and -1b than to IFN-α.</p>	<p>Well established agent with defined but complex safety profile. Clinicians experienced in managing side effects should be consulted e.g. those who have treated hepatitis C virus (HCV) infection and multiple sclerosis.</p>	<p>Several different interferons are available for systemic administration, for different licensed indications.</p> <p>There are insufficient data to strongly recommend a particular preparation, although IFN-β appears more promising based on available data.</p> <p>Injection: included as an arm in REMAP-CAP trial (recruiting)</p> <p>Nebulised: included as an arm in the UK RECOVERY trial (recruiting).</p>

Key references

Al Ghamdi M, Al Ghamdi KM, Ghandoorah Y, Alzahrani A, Salah F, Alsulami A, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis*. 2016 Apr 21;16:174.

Arabi YM, Allothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon- β 1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials*. 2018 Jan 30;19(1):81.

Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. *Clin Infect Dis*. 2019 Jun 25. pii: ciz544. doi: 10.1093/cid/ciz544. [Epub ahead of print]

Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. *Antivir Chem Chemother*. 2006;17(5):275-84.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *NEJM*. 2020 Mar 18. [Epub ahead of print]

Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect*. 2013 Dec;67(6):606-616.

Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon- β 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis*. 2015 Dec 15;212(12):1904-1913.

Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J*. 2003 Dec;9(6):399-406.

Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol*. 2004 Sep;31(1):69-75.

Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Kao RY, et al. Group HUSS. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004 Mar;59(3):252-256.

de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014 Aug;58(8):4875-4884.

de Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RWAL, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon- α treatment. *J Gen Virol*. 2013 Aug;94(Pt 8):1749-60.

de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A*. 2020 Feb 13. [Epub ahead of print].

Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, et al. Treatment with interferon- α 2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat Med*. 2013 Oct;19(10):1313-1317.

Gautret P, Lagier J-C, Parola P, Hoang V T, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J Antimicrob Agents*. In Press, Journal Pre-Proof [Available online 20 March 2020, 105949].

Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem*. 2020 Feb 24. [Epub ahead of print]

Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol*. 2011 May;23(3):278-281.

Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun*. 2004 Oct 8;323(1):264-268.

Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA*. 2003 Dec 24;290(24):3222-8.

Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014 Nov;14(11):1090-1095.

Park SY, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect*. 2019 Jan;101(1):42-46.

Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses*. 2018 May 17;10(5):268.

Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017 Jun 28;9(396):eaal3653.

Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020 Jan 10;11(1):222.

Song S., Zhang D, Qian Z, Li T, Shen Y, Lu H. [Abstract] To evaluate the efficacy and safety of hydroxychloroquine (HCQ) in the treatment of patients with common coronavirus disease-19 (COVID-19). *Journal of Zhejiang University*. 2020 Mar.

Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006 Sep;3(9):e343.

Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res.* 2020 Mar. [Epub ahead of print].

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020 Mar;30(3):269-271.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020 Mar 11. pii: S0140-6736(20)30566-3. doi: 10.1016/S0140-6736(20)30566-3. [Epub ahead of print],

Acknowledgement

This appendix is taken from 'Treatment of COVID-19: Interim Decision Support Tool for clinicians' (30 March 2020, Version 2.0) authored by Meera Chand¹, Jake Dunning², Michael Jacobs². The authors wish to thank Professor Frederick Hayden, University of Virginia School of Medicine, for his expert comments and advice on a previous version.

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