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

Interim Support for clinicians in England

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File name:	CTAG/PS/COVID19/Interimsupport
Version number:	1.0
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:	23 March 2020
Review date:	30 March 2020

Contents

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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provides interim supporting information on the pharmacological management of adult patients with COVID-19 and will be superseded when specific guidance is published by NHS England, Department of Health and Social Care or Public Health England.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 comparative trial evidence that any treatment beyond best supportive care delivers improved outcomes for patients with COVID-19 as of 22 March 2020.[2,3]

2.2. Several investigative agents have potential to be repurposed for the management of COVID-19[1,2]; the risk-benefit of these agents have been summarised in the 'Treatment of COVID-19 with investigational antiviral agents: Interim Decision Support Tool for clinicians'[2] – refer to Appendix 1.

2.3. Investigative agents should only be used in the context of a clinical trial using supplies allocated for clinical trial use. As relevant trials open, sites are encouraged to engage with their R&D services to adopt such studies to deliver treatments – refer to Section 3.

2.4. Where possible, hospitals in England that are managing COVID-19 cases should establish capacity for recruitment into clinical trials.

2.5. The RECOVERY trial (UK study; standard of care *versus* lopinavir/ritonavir vs. interferon beta-1a vs. dexamethasone) is HRA approved and opened to recruitment on 20 March 2020.

2.6. 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 (Kaletra®)
- Immune Modulation therapy: evaluating no immune-modulating therapy (and no placebo), interferon-beta-1a, and interleukin-1 receptor antagonist (anakinra)

2.7. For clinicians unable access investigative agents within the context of a clinical trial, remdesivir can be considered for patients who meet the Gilead expanded access programme eligibility criteria – refer to Section 4.

2.8. 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.

2.9. 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).

2.10. 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.

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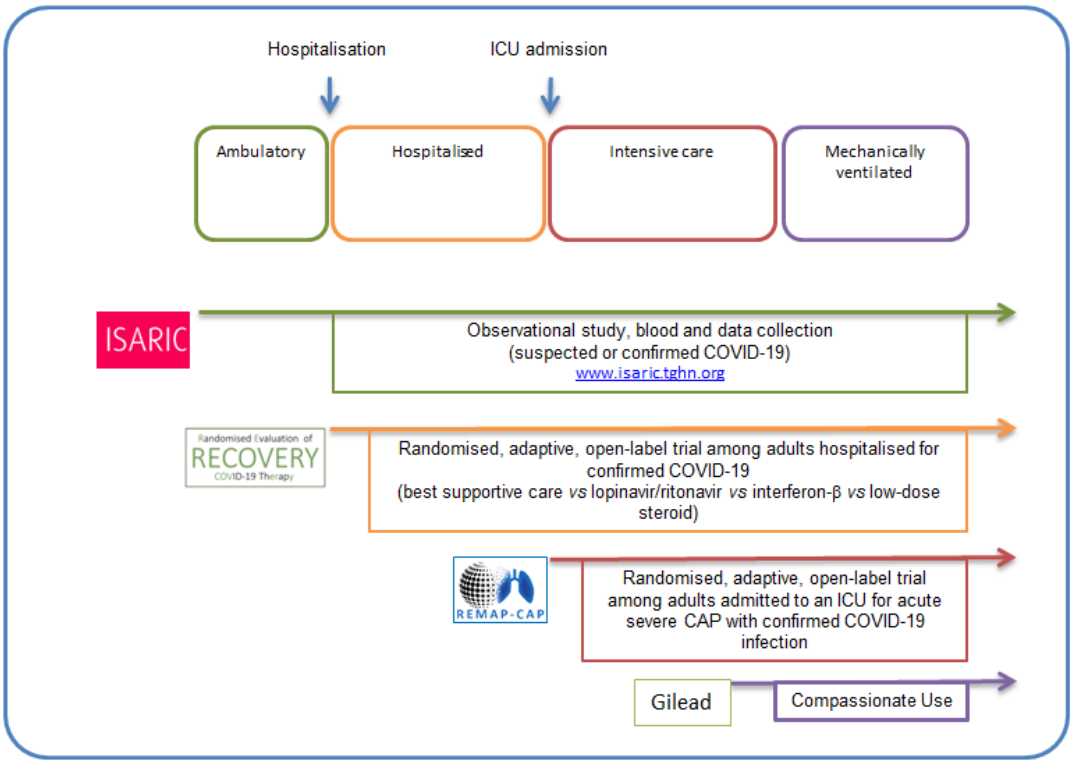

Figure 1: Active UK Clinical Studies as at 23 March 2020 (Figure will be updated as new studies are activated for UK patient recruitment). Participation for COVID-19 trials will be through adoption at local sites, information should be available at through local Research and Development Offices. There 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. The following interventional clinical trials and national observational studies are active in the UK for recruitment for hospitalised patients:

- RECOVERY trial (UK study; standard of care *versus* lopinavir/ritonavir vs. interferon beta-1a vs. dexamethasone)
- REMAP-CAP (international critical care study, UK sites; expanded to include COVID-19-specific arms for standard of care *versus* lopinavir/ritonavir (Kaletra®) and standard of care *versus* interferon-beta-1a, and interleukin-1 receptor antagonist (Anakinra®)
- ISARIC-CCP UK Case Record Forms (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19

3.2. The following interventional clinical trials and national observational studies are emerging or proposed in the UK:

- DISCOVERY trial (WHO pan-European; standard of care *versus* standard of care + remdesivir *versus* standard of care + lopinavir/ritonavir *versus* standard-of-care + lopinavir/ritonavir + Interferon beta-1a)
- Proposal to amend the REALIST trial (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab
- ACTT trial (remdesivir *versus* standard-of-care)

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4. Gilead expanded access programme

Remdesivir infusion (formerly GS-5734; unlicensed medicine)						
Eligibility criteria*	**Exclusion criteria***	**Dose**	**Duration**	**Special precautions**	**Drug specific monitoring**	**Supply route***
Hospitalised, confirmation of SARS-CoV-2 infection by PCR and mechanical ventilated[4]	Evidence of multi-organ failure; Pressor requirement to maintain BP; ALT levels > 5x upper limit of normal; Creatinine clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration, no concurrent experimental antiviral agents for COVID-19 (prior use is OK)[4]; Pregnancy**	Adult and adolescent (≥ 40 kg) - 200 mg IV loading dose on Day 1 followed by 100 mg IV once-daily on Day 2 onwards. Infuse dose over 30 minutes[5] Dosing information may vary to the above and should be guided by ID/Virology and dosing protocol provided by Gilead.	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.[5]	No information for dose adjustment in liver and renal impairment (likely would be excluded from the programme)	Limited information available, generally well tolerated. Reversible Grade 1 or 2 ALT or AST elevation observed.[4] Daily monitoring of renal (creatinine and BUN) and liver (ALT, AST) functions should be performed[5]	Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/. Any communication with Gilead should include UKICOVID-19@gilead.com[3]

Further information: https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1

**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.*

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5. References

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2. UK Airborne High Consequence Infectious Diseases Network. Treatment of COVID-19 with investigational antiviral agents: Interim Decision Support Tool for clinicians. (2020).

3. Miro, J. M. *et al.* Immune Reconstitution in Severely Immunosuppressed Antiretroviral-Naive HIV-1-Infected Patients Starting Efavirenz, Lopinavir-Ritonavir, or Atazanavir-Ritonavir Plus Tenofovir/Emtricitabine: final 48-Week Results (The Advanz-3 Trial). *Journal of acquired immune deficiency syndromes (1999)* **69**, 206-215 (2015).

4. Email communication with Gilead (Dr Shayon Shalehi). (2020).

5. 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).

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

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

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- 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)
- Dr Sanjay Bhagani (Consultant, Infectious Diseases; Royal Free London)
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- Dr Michael Beadsworth (Consultant, Infectious Diseases; Liverpool)
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- Dr Sarah Logan (Consultant, Infectious Diseases; UCL Hospitals)
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Appendix 1: Treatment of COVID-19 with investigational antiviral agents: Interim Decision Support Tool for clinicians

Interim Decision Support Tool for clinicians

16 March 2020 v1.0

Meera Chand, Jake Dunning, Michael Jacobs
on behalf of the UK Airborne High Consequence Infectious Diseases Network

The authors wish to thank Professor Frederick Hayden, University of Virginia School of Medicine, for his expert comments and advice.

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1 Document scope

This evolving document is intended to provide an overview of available evidence and experience on investigational therapeutics for UK clinicians treating confirmed cases of COVID-19.

It was produced on behalf of the UK Airborne High Consequences Diseases network, for the use of UK clinicians. 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. Further agents and therapeutic combinations will be added to updated versions of this document. 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. WHO clinical management guidance is available at: https://tinyurl.com/rh99jm7

2 Background

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

There are currently very limited data on antiviral treatments for SARS-CoV-2, and so we draw inferences from data for other betacoronaviruses that cause severe respiratory disease in humans: SARS-CoV and the less closely related MERS-CoV. There are some differences between these viruses that are not yet sufficiently defined to understand their clinical relevance.

There are increasing data on the clinical course and viral dynamics in COVID-19, but it is not yet clear how these impact on the best timing and efficacy of specific treatments.

3 Principles for using experimental therapies

Treatment with investigational agents should occur within the context of controlled intervention trials if at all possible.

Monitored experimental use of therapy (“compassionate use”) may be appropriate if the treating clinician judges that the potential for benefit is likely to outweigh the risk. This document aims to help clinicians with these assessments.

In general, monitored experimental use of therapy should always be accompanied by systematic data collection, in order to help inform future guidance. The ISARIC-WHO Case Record Form is available here: https://isaric.tghn.org/covid-19-clinical-research-resources

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4 Therapies under consideration

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 
SARS-CoV	Human observational study	
MERS-CoV	Nonhuman primate experimental	
Other betacoronavirus	Small animal experimental	
	In vitro	
	Theoretical	Least evidence

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 COVD-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.

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 (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**
Siv; Miv; S2iv Sa; Ma Several non-UK S2c studies in progress and expected to report Apr 2020	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 *in vitro*, 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 *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	Inhibits SARS-CoV-2 replication in Vero cells with a low micromolar EC50 value.	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.	Limited supply available for compassionate use (March 2020). Use restricted to severely ill patients. Compassionate use programme details at: https://rdvcu.gilead.com

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Lopinavir/ritonavir				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Ma Sc Several non-UK S2c studies in progress and expected to report imminently	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. Direct comparison between remdesivir, lopinavir/ritonavir, and interferon-beta *in vitro* and in mouse models of MERS-CoV infection demonstrated greater virological, clinical and histopathological benefit with remdesivir.	Unpulished 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. An open-label RCT of lopnavir-ritonavir in hospitlalized COVID-19 patients has been completed but results are not yet publically available.	Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common. Note multiple significant drug-drug interactions.	Routinely available (licensed for the treatment of HIV-1 infection).

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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

Chloroquine (CQ)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; S2iv	Inhibitory *in vitro* for SARS-CoV but the selective index is low. In one murine model of SARS intraperitoneal chlorquine was ineffective in inhibiting lung virus titers. For multiple other viruses, potent *in vitro* 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 chickungunya infection (which is unrelated to SARS-CoV-2), CQ treatment resulted in worse outcomes, despite promising antiviral activity *in vitro*.	Effective inhibition of SARS-CoV-2 replication *in vitro.* Early announcements from China have reported significant clinical benefit of CQ treatment in COVID-19, but supporting data awaited.	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).	Routinely available (various licensed indications, including malaria and rheumatoid arthritis).

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Interferon (systemic)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc	Type I (α, β), type II (γ), and type III (λ) IFNs all show activity against SARS-CoV in extensive *in vitro* studies. Type I (α, β) IFNs have shownactivity 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. *In vitro*, 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.	Unpublished in vitro data indicate that SARS-CoV is more susceptible to IFN- β-1a and -1b than to IFN-α.	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.	Several different interferons are available for systemic administration. There are insufficient data to strongly recommend a particular preparation, although IFN-β appears more promising based on available data.

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Consultation

Rapid review was undertaken by the UK Airborne HCID Network lead clinicans:

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- Nicholas Price, Guys and St Thomas' NHS Foundation Trust
- Matthias Schmid, The Newcastle upon Tyne Hospitals NHS Foundation Trust
- Anne Tunbridge, Sheffield Teaching Hospitals NHS Foundation Trust

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