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Position Statement: Use of investigational antiviral medicines for COVID-19 in adults

Interim support for UK hospital clinicians

Document management

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Contents

Abbreviations

Abbreviation	Meaning
CMO	Chief Medical Officer
NIHR	National Institute for Health Research
R&D	Research and Development
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SoC	Standard of Care

Key messages

- There are no antiviral medicines approved to treat or prevent disease caused by human coronaviruses. There is no published randomised controlled trial evidence that any treatment beyond best supportive care delivers improved outcomes for patients with COVID-19.
- Investigative antiviral medicines should be used in the context of a clinical trial.
- For clinicians unable to access investigative medicines within the context of a clinical trial, Gilead have a remdesivir Expanded Access Programme and organisations can contact Gilead to discuss participation in this programme. A Compassionate Access Programme is also available.
- 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.
- Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

1. Aim

1.1. To provide interim supporting information on the appropriate use of investigational antiviral medicines for the treatment and prevention of COVID-19 in adults, in the hospital setting. This position statement will be updated in response to relevant developments and superseded when specific national guidance is published by UK health technology assessment bodies (e.g. National Institute for Health and Care Excellence, All Wales Medicines Strategy Group or Scottish Medicines Consortium).

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 in patients with COVID-19.

2. Treatment: Supporting information

2.1. There are no antiviral medicines approved to treat or prevent human coronaviruses.[1] There is no published randomised controlled trial evidence that any treatment beyond best supportive care delivers improved outcomes for patients with COVID-19 as of 18 May 2020. [2,3(p1)]

2.2. Several investigative antiviral medicines have potential to be repurposed for the management of COVID-19;[1,2] the evidence-base for these medicines is summarised in Appendix 1.

2.3. Investigative antiviral medicines should be used in the context of a clinical trial[a,b,c]. The off-label or 'non-trial' use of medicines should be avoided because medicines currently within the NHS supply chain are needed for the patients already prescribed within licensed indications.[6]

2.4. Hospitals managing COVID-19 cases should make every effort to enrol COVID-19 patients in national priority clinical trials[5,7] – refer to Section 4.

2.5. The following prioritised trials for investigative antiviral medicines for hospitalised patients with COVID-19 are open to recruitment:

- RECOVERY (in hospital trial; UK study open to all Trusts)
- REMAP-CAP (critical care trial; international with UK sites) added immunomodulatory and antiviral domains for COVID-19
- ACTT (in hospital severe infection trial; international with UK sites)
- GS-5774 (in hospital moderate infection trial; international with UK sites)
- GS-5773 (in hospital severe infection trial; international with UK sites)
- SNG016 (in hospital moderate infection trial; UK study)

2.6. For clinicians unable to access investigative medicines within the context of a clinical trial, Gilead have a remdesivir Expanded Access Programme and organisations can contact Gilead to discuss participation in this programme. A Compassionate Use Programme (CUP) is also available – refer to Section 5. Enrolment into ISARIC-CCP is encouraged for patients accessing the CUP as data for pregnant women and young children will not be available from interventional clinical trials.

2.7. 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.

2.8. Patients diagnosed with COVID-19 in the community may be admitted into hospitals receiving an investigative antiviral 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. Patients may be diagnosed with COVID-19 whilst receiving investigative prophylactic treatment e.g. COPCOV trial. When such a patient would otherwise be eligible for enrolment into an interventional treatment trial discontinuation of the prophylactic agent should be discussed with the Principal Investigator responsible their treatment.

2.10. Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

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[a] No restriction should be imposed for the use of these medicines within their licensed and/or recognised indications e.g. hydroxychloroquine for systemic lupus erythematosus, or lopinavir/ritonavir for HIV.

[b] MHRA recommends chloroquine and hydroxychloroquine are only used for the treatment and prevention of COVID-19 within the context of a clinical trial[4]

[c] Chief Medical Officers strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible[5]

2.11. Supporting information for the use of immunomodulators for COVID-19 associated hyperinflammation (including anakinra, tocilizumab, sarilumab and ruxolitinib) is available at https://www.ctag-support.org.uk/immunomodulators

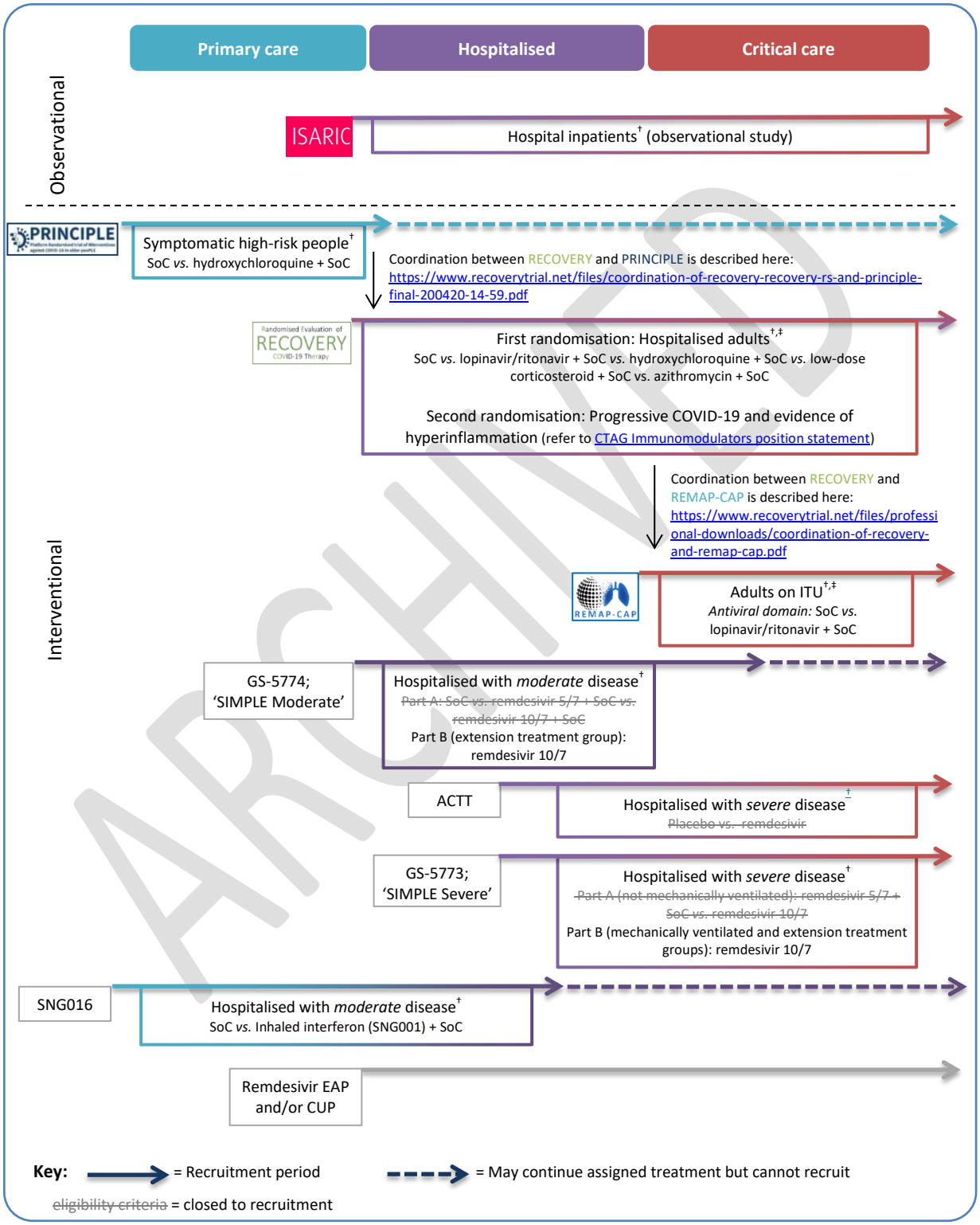

Figure 1: Antiviral components for recruiting UK clinical studies as at 22 May 2020 (excludes trials of antiviral prophylaxis). SoC; standard of care. EAP; expanded access programme. CUP; compassionate use programme. † Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/. ‡ These studies also include domains which are outside the scope of this document (e.g. immunomodulators, anticoagulation).

3. Prophylaxis: Supporting information

3.1. Refer to information in 2.1 to 2.4

3.2. The following prioritised trials for investigative antiviral medicines for the prevention of COVID-19 are open to recruitment:

- COPCOV (healthcare workers or hospitalised patients or relatives exposed or potentially exposed or other high risk groups; international with UK sites)

4. UK clinical studies

4.1. The Chief Medical Officers recommends that any treatment given for coronavirus other than general supportive care and treatment for underlying conditions should currently be as part of a trial, where that is possible[5]

4.2. NIHR is working with the Department of Health and Social Care (DHSC) to coordinate the national research agenda[8].

4.3. Organisations should prioritise support for studies which have been nationally prioritised[8]. Non-prioritised research should continue, subject to it not having a negative impact on the system's ability to recruit participants and provide the resources needed to support priority clinical studies[7].

4.4. A complete list of nationally prioritised research studies for COVID-19 is available on the NIHR website https://www.nihr.ac.uk/covid-studies/

4.5. Antiviral interventional studies and observational studies of relevance to COVID-19 treatment as summarised below:

- Table 1: Active studies
- Table 2: Proposed studies (not all are nationally prioritised)

Table 1: Recruiting in the UK - Antiviral interventional clinical trials and observational studies

Status	Trial		Cohort	Interventions
Recruiting	Interventional	PRINCIPLE[†] (UK study; ISRCTN86534580)	Primary care; higher risk individuals (≥65 years or ≥50 years with specified illness) with suspected or confirmed COVID-19	– SoC – Hydroxychloroquine + SoC
		RECOVERY[†,‡] (UK study, open to all Trusts; ISRCTN16912075)	First randomisation: Hospital inpatients; adults and paediatrics (any age) with suspected or confirmed COVID-19 Second randomisation: Progressive COVID-19 (SpO2 <92% on room air or requiring oxygen) and CRP ≥75 mg/L	First randomisation[§]: – SoC – Lopinavir/ritonavir + SoC – Hydroxychloroquine + SoC – Low dose corticosteroids + SoC – Azithromycin + SoC Second randomisation[§]: SoC vs. tocilizumab + SoC both in addition to the first randomisation (refer to CTAG Immunomodulators position statement) [§] *Not all paediatric age groups are eligible for all treatment arms, refer to trial protocol (Appendix 3) for arm specific eligibility criteria.*
		REMAP-CAP[†,‡] (International study with UK sites; NCT02735707)	Critical care; adults (≥18 years) with suspected or confirmed COVID-19	Antiviral domains for COVID-19: – SoC – Lopinavir/ritonavir + SoC Note: three other COVID-19 domains are available; prolonged macrolide therapy, alternative corticosteroid strategies, immune modulation therapy.
		ACTT[†] (International study with limited UK sites; NCT04280705)	Hospital inpatients (≥18 years); adults with confirmed COVID-19 (severe disease)	~~– Placebo + SoC~~ ~~– Remdesivir + SoC~~
		GS-5774[†] (International study with UK sites; NCT04292730)	Hospital inpatients; adult or adolescents (≥12 years) weighing ≥40 kg with confirmed COVID-19 (moderate disease)	~~Part A:~~ ~~– SoC~~ ~~– Remdesivir 5 days + SoC~~ ~~– Remdesivir 10 days + SoC~~ Part B (extension treatment group): – Remdesivir 10 days + SoC
		GS-5773[†] (International study with UK sites; NCT04292899)	Hospital inpatients; adult or adolescents (≥12 years) weighing ≥40 kg with confirmed COVID-19 (severe disease)	~~Part A (not mechanically ventilated):~~ ~~– Remdesivir 5 days + SoC~~ ~~– Remdesivir 10 days + SoC~~ Part B (mechanically ventilated and extension treatment groups): – Remdesivir 10 days + SoC

Status	Trial		Cohort	Interventions
		SNG016† (Phase II study, UK study with limited sites[9]; 2020-001023-14) *This study is listed as SARS-CoV-2 infection on the NIHR website*	– Hospital inpatients; adults (≥18 years) with confirmed COVID-19[10]	• Placebo + SoC • Inhaled interferon (SNG001) + SoC
		COPCOV† (UK study; NCT04303507)	– Preventative treatment for healthcare workers (≥16 years)	• Placebo • Hydroxychloroquine
	Observational	ISARIC-CCP† (International study; ISRCTN66726260)	– Hospital inpatients; confirmed COVID-19.	• N/A – study has multiple objectives (see protocol); including describing clinical features and response to treatments. Case Record Forms (CRF) are available.

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/ ‡ These studies also include domains which are outside the scope of this document (e.g. immunomodulators). ~~treatment arms~~ = closed to recruitment

Table 2: Proposed in the UK - Antiviral interventional clinical trials

Status	Trial		Cohort	Interventions
Proposed	Interventional	CROWN CORONATION (International study with UK sites; NCT04333732)	Preventative treatment for healthcare workers	• Low-dose chloroquine • Mid-dose chloroquine • High-dose chloroquine • Placebo
		ACCORD-2‡ (UK Phase II clinical trials program)	Potentially different for each sub-protocol	Multiple candidate agents as treatments for COVID-19 (each with their own subprotocol). No subprotocols for investigative antivirals however refer to CTAG Immunomodulators position statement for status of investigative immunomodulators.

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/ ‡ These studies also include domains/subprotocols which are outside the scope of this document (e.g. immunomodulators).

5. Gilead compassionate use programme

Remdesivir infusion (formerly GS-5734; unlicensed medicine)						
Eligibility criteria[10]	**Exclusion criteria**[11]	**Dose**	**Duration**	**Special precautions**	**Drug specific monitoring**	**Supply route**
• Pregnant women or Children ≤18 years of age • Hospitalization • Confirmed COVID-19 • Severe manifestation of disease	• Evidence of Multi-organ failure • Pressor requirement to maintain blood pressure • ALT levels > 5 X ULN • Creatinine Clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration • Concomitant administration of other investigational medicines for COVID-19 is not permitted while receiving remdesivir.	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; see Medusa for full details https://injmed.wales.nhs.uk/IVGuideDisplay.asp Dosing information may vary to the above and should be guided by ID/Virology and dosing protocol provided by Gilead. Support for the management of paediatrics is not within scope. For paediatric dosing, please contact Gilead directly.	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.[12]	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[12]	Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/. Any communication with Gilead should include UKICOVID-19@gilead.com
Further information: https://www.who.int/ebola/drc-2018/summaries-of-evidence-experimental-therapeutics.pdf?ua=1						

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Membership and provenance

The support contained within this document is provided by the COVID-19 Therapeutics Advice & Support Group (CTAG) antiviral subgroup.

The provenance for this subgroup is the Network of High Consequence Infectious Diseases (HCID). In March 2020, the collaborative expanded to include experts in Infectious Diseases from other Provider Trusts.

Document control

Date	Version	Amendments
23 Mar 2020	1.0	New document
23 Mar 2020	1.1	Updated Gilead remdesivir Compassionate Use Programme 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.
07 Apr 2020	2.1	Updated title to reflect updated scope (antiviral use in hospitals). Updated Section 2, 3 and Figure 1 with new trials and trial status. Included reference to CMO letter. Reformatting throughout. Added BIA and UKCPA-PIN logos (with permission).
08 Apr 2020	2.2	Updated membership & provenance. Corrected typo (2.5).
18 Apr 2020	2.3	Updated arms of RECOVERY study. Provided additional information for Gilead remdesivir Compassionate Use Programme. Updated references and web links. Updated evidence summaries in Appendix 1. Added azithromycin and inhaled interferon tables to Appendix 1.
01 May 2020	2.4	Addition of 'Key messages' and 'Abbreviations'. Emphasised importance of avoiding off-label use of investigational antivirals. Added reference to 'CTAG: Position Statement on the use of investigational immunomodulatory agents for COVID-19 in adults'. Format change to clinical trials tables. Change SNG016 and COPCOV from 'proposed' to 'active'. Added GenOMICC study. Updated evidence summaries in Appendix 1 (remdesivir; nebulised interferon; added EMA statement for chloroquine/hydroxychloroquine).
19 May 2020	2.5	Included reference to CMO letter and COVID-19 Yellow Card reporting. Updated evidence summaries in Appendix 1 (interferon). Updated support for patients diagnosed with COVID-19 whilst receiving investigative prophylactic treatment. Removed reference to GenOMICC as out of scope. Updated RECOVERY eligibility criteria to include paediatrics. Changed COPCOV from chloroquine to hydroxychloroquine. Changed CROWN CORONATION from hydroxychloroquine to chloroquine. Removed DisCoVeRy from Table 2.

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.

Methods

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

We reviewed the available data on treatment of betacoronaviruses but restricted the search to investigational antiviral agents being used, or considered, within the context of UK clinical trials. This includes all investigational antiviral agents identified in the NIHR list of nationally prioritised studies.

We broadly hierarchised the evidence according to the following matrix and considered the available safety data.

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

Evidence summary

Summaries are provided for investigational antiviral treatments being used, or considered, within the context of UK clinical trials.

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

1) For compassionate use, benefit may exceed risk (Table 3)
2) Inadequate data to recommend compassionate use currently, await further data (Table 4)

Table 3: Evidence base for specific therapies for SARS-CoV-2 infection: For compassionate use, benefit may exceed risk

*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; S2c	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.	Observational cohort study of compassionate use programme among people with severe COVID-19 found that 36/53 patients with outcomes (68%) showed clinical improvement. However, no control arm was included and no outcome data available for 8 participants[13]. A double-blinded RCT in China compared remdesivir to placebo among 237 adults with severe COVID-19 (defined as radiologically-confirmed pneumonia and either SpO2 ≤94 % on air or PaO2/FiO2 ratio ≤300), ≤12 days from symptom onset to enrolment[14]. At 28 days, remdesivir was not associated with difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0·87–1·75]) or overall mortality (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group). In a post-hoc analysis, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration ≤10 days at enrolment (hazard ratio 1.52 [0·95–2·43]). However, the trial was underpowered. Preliminary results (reported in a press release and FDA-issued Emergency Use Authorization) from the NIAID-sponsored ACTT trial of 1063 patients show median time to recovery of 11 days in the remdesivir group, vs. 15 days in the placebo group (hazard ratio 1.31; 95% CI 1.12-1.54, p<0.001). Mortality was 8.0% for the remdesivir group versus 11.6% for the placebo group (p=0.059).[15] Full results awaited. Preliminary results (reported in a press release and FDA-issued Emergency Use Authorization) suggest that results from the 'SIMPLE Severe' trial of 397 patients show 10-day and 5-day courses of remdesivir achieve similar improvements in clinical status on Day 14 (odds ratio 0.75 [0.51 – 1.12]).[15,16] Full results awaited.	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. No new safety signals detected in the RCT from China in COVID-19[14].	Limited supply available for compassionate use (March 2020) and use is restricted to specific patient groups; refer to compassionate use programme details at: https://rdvcu.gilead.com Multiple international clinical trials underway (manufacturer's website): https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials

Table 4. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommend 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	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.	Unpublished data indicate that lopinavir is inhibitory at uM concentrations for SARS-CoV-2 in Vero cell culture. An exploratory RCT assessing lopinavir/ritonavir or arbidol to among 86 hospitalised adults with mild/moderate COVID-19 reported no differences between arms in time from positive-to-negative viral conversion using RT-PCR (mean 9.0 days (SD 5.0) in the LPV/r group, 9.1 (SD 4.4) in the arbidol group and 9.3 (SD 5.2) in the control group), though the trial was underpowered.[17] 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 (hazard ratio 1.31; 95% CI 0.95 to 1.80). 28-day mortality was similar in the lopinavir–ritonavir group and the standard-care groups (19.2% vs. 25.0%; difference −5.8; 95% CI, −17.3 to 5.7). Lopinavir-ritonavir recipients spent less time in hospital (12 vs. 14 days) and less time in intensive care (6 vs. 11 days).[18(p19)] An open-label multicentre RCT in Hong Kong comparing treatment with subcutaneous IFNβ-1b, ribavirin & lopinavir/ritonavir, to lopinavir/ritonavir alone (n=41), in hospitalized patients with mild-moderate COVID-19 is described in the Interferon (systemic) table.[19]	Well established agent with well understood toxicity profile. Gastrointestinal side effects are very common. Note multiple, significant drug-drug interactions.	Licensed for the treatment of HIV-1 infection. Included as an arm in the UK RECOVERY trial and REMAP-CAP trial (recruiting).

Chloroquine (CQ) / Hydroxychloroquine (HCQ)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; S2iv; S2c	Inhibitory *in vitro* 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 *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*.[20] An abstract from China reported a 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.[21]A small trial from China (n=22) compared CQ with lopinavir-ritonavir.[22] Patients treated with CQ were reported to have earlier improvement in chest CT appearances, and were discharged earlier (100% vs 50% at day 14). It is not clear if the study was randomised, and it was not powered to detect clinical outcomes. Two randomised trials from China have compared HQ with standard of care in hospitalised patients with mild-moderate COVID-19. The first (n=150, open-label[23]) reported no difference between arms in the probability of viral negative conversion by 28 days (using RT-PCR): 85.4% (95% CI 73.8-93.8%) vs 81.3%, (71.2-89.6%). This trial identified higher rates of adverse events (30% versus 9%), mainly gastrointestinal, in the HCQ arm. There were low rates of progression to severe disease in both arms and no mortality. The second, released as a preprint (n=62, blinding unclear[24]), reported a faster time to clinical recovery with HCQ, defined by normalisation of body temperature (1 day quicker) and faster time to improvement of pneumonia on chest CT (80.6% vs 54.8% improved at day 6). Eventual clinical outcomes are not reported, and it is stated that other antiviral treatments are used in the standard of care arm, but these are not specified. Two large observational studies from the USA report associations between use of HCQ and intubation or mortality. The first study describes 1446 consecutive patients, 58.9% of whom received HCQ. These patients tended to be more severely unwell at baseline (Geleris et al., 2020). There was no association between HCQ and a composite endpoint of intubation or death. The second retrospective study describes 1438 patients treated with either HCQ, azithromycin, both or neither (Rosenberg et al., 2020). Patients who received pharmacological treatments were more unwell at baseline. An aggregate 70% of patients received a HCQ-containing regimen. There was no association between HCQ and mortality.	Well established agent, defined safety profile as antimalarial drug; however, safety in acute viral illness is not established and studies raise concerns. A publication reports findings from a randomised trial of CQ in Brazil, which stopped recruitment to its higher dose arm (600mg BD for 10 days) early, due to a safety signal for QTc prolongation and fatality.[25] The EMA issued a public health statement on 23/04/2020 cautioning clinicians to closely monitor QTc intervals in patients receiving HCQ/CQ, particularly at higher doses or when taken in combination with azithromycin.[26]	Various licensed indications, including malaria and rheumatoid arthritis. Included as an arm in the UK RECOVERY trial and PRINCIPLE trial (recruiting).

Interferon (systemic)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv Sa; Ma Sc; Mc S2iv; S2c	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 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. *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. A preprint reports in vitro data indicating that SARS-CoV2 is more susceptible than SARS-CoV to pre-treatment with IFNα-, when cultured in Vero cells.[27] An open-label multicentre RCT in Hong Kong compared treatment with subcutaneous IFNβ-1b, ribavirin & lopinavir/ritonavir (n=86), to lopinavir/ritonavir alone (n=41), in hospitalized patients with mild-moderate COVID-19 (Hung et al., 2020).[19] Patients in the intervention group had significantly shorter times to positive-to-negative viral conversion of NP swabs (using RT-PCR)s: 7 days versus 12 days, HR 4.37. Significant findings are also reported for secondary outcomes including shorter time to clinical recovery in the intervention group (4 days versus 8 days) and shorter length of hospital stay (9 days versus 14.5 days). The trial was not blinded and observer bias may confound subjective clinical endpoints. The majority of patients had mild disease (only 13% required supplemental O2) and no mortality was observed, so it is not clear if findings can be generalized to patients with severe disease. There is heterogeneity in the intervention arm, as IFNβ treatment was only used in patients randomized to the control group if they were within 1 week of symptom onset. A subgroup analysis indicated that the apparent benefits in the intervention group were only seen in the group of patients treated with IFNβ within the first week of symptoms. Further trials comparing IFNβ with standard of care or placebo would be required to confirm this finding.	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, for different licensed indications. There are insufficient data to strongly recommend a particular preparation, although IFN-β appears more promising based on available data. IFN-β injection: included as an arm in the immune modulation domain of REMAP-CAP trial (recruiting)

Interferon (nebulised)				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Siv; Miv S2iv; S2c	Please see "Interferon (systemic)" for a summary of *in vitro* and animal model data regarding IFN, SARS-CoV and MERS. To date, there have been no animal studies reported investigating inhaled interferon in models of SARS or MERS. To date, there have been no clinical trials reported of inhaled interferon therapies in SARS or MERS.	Please see "Interferon (systemic)" for a summary of *in vitro* data regarding IFN and SARS-CoV-2. To date, there have been no animal studies of inhaled interferon in models of SARS-CoV-2. An retrospective study in China assessed patients classified as having moderate (n=22) or severe (n=21) COVID-19, who were treated with nebulized IFNα-2b alongside other interventions including unspecified oral antivirals & ribavirin.[28] Patients classified as having mild disease (n=12) had not received IFN. The moderate group were combined with patients with mild disease for analysis, in comparison to the severe group. Outcomes were similar in the 2 groups with resolution of clinical manifestations by 2 weeks in 85.7% of patients in the severe group, and 91.2% patients in the mild/moderate group). No conclusions can be drawn as the study was not randomized and analysis was not stratified by use of interferon. A preprint reports a retrospective study in China (n=77) which assessed hospitalized patients treated with nebulized IFN-α2b versus those treated with the oral antiviral umifenovir (arbidol), versus those treated with both in combination.[29(p19)] The authors report significantly shorter times to viral clearance on throat swabs, and lower circulating inflammatory markers (IL-6 and CRP), in the groups who received nebulized IFNα-2b. However, no clinical outcomes are reported, and findings may be confounded as the study was not randomized or blinded. Furthermore, the patients in the group who did not receive IFN treatment were significantly older than the IFN-treated groups (median age 64.5 versus 40.4 or 41.3) and had higher rates of comorbidities (54% versus 15.2% or 14.3%).	No reported safety data in the context of human coronaviruses. A phase II human trials of SNG001 (nebulized IFN β-1a), in individuals with a background of viral-induced asthma who had new cold-like symptoms, reported that it was well tolerated with no safety signals flagged.[30]	One clinical formulation made by Synairgen, SNG001, a nebulised formulation of IFNβ-1a. It is not currently available in the UK for compassionate use but this may be subject to change (https://www.synairgen.com/) . Phase II clinical trial of SNG001 in COVID-19 sponsored by Synairgen, SNG016, is currently recruiting in the UK (EudraCT number - 2020-001023-14, https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001023-14/GB)

Azithromycin				
Studies performed*	**Data: SARS, MERS and other**	**Data: SARS-CoV-2**	**Safety profile**	**UK feasibility**
Mc, S2c	Macrolide antibiotic. Reported to have *in vitro* activity against the unrelated RNA virus Zika virus (ZIKV) in cultured glial cells & astrocytes. Reported to have *in vitro* activity against the unrelated virus rhinovirus in cultures of bronchial epithelial cells. Reported to have *in vitro* activity against influenza virus by blocking viral internalisation, and was effective in a mouse model of influenza. Reported to have *in vitro* activity against the unrelated RNA virus Ebola virus (EBOV), but was not effective in small animal models of EBOV infection. Mechanisms of antiviral activity have not been identified. To date, there have been no reported *in vitro* studies testing the effect of azithromycin against SARS-CoV or MERS-CoV. To date, there have been no reported animal models testing the effect of azithromycin on SARS or MERS. An observational cohort study of 349 critically ill MERS patients in Saudi Arabia, of whom 136 (39%) received macrolide therapy, showed no association of macrolide therapy with 90-day mortality or time to viral clearance (using RT-PCR).	To date, there have been no reported in vitro studies or animal models testing the effect of azithromycin on SARS-CoV2. Azithromycin was given in two small, open-label SARS-CoV-2 studies in France.[31,32] In the first non-randomised study, 20 patients receiving HCQ (6 of whom received azithromycin) were compared to 16 controls with a reduction in viral load reported; however, there were no quantitative PCR results, 6 patients were excluded, no ITT analysis, and trial was underpowered. In the second observational cohort study, all patients received HCQ and azithromycin (n=80), reporting a reduction in viral load and clinical improvement in most patients. However, there was no control group, unclear eligibility criteria, and it was underpowered for clinical outcomes.	Well established agent with well understood toxicity profile including gastrointestinal upset (common) and QT prolongation (uncommon).	Various licensed indications as an antimicrobial. Included as an arm in the UK RECOVERY trial. Prolonged macrolide therapy is also an existing arm in REMAP-CAP trial, but with immunomodulatory rather than antiviral intent.

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