Royal College of Physicians

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Position Statement:
Use of <u>antiviral</u> medicines for COVID-19 in adults

Interim support for UK hospital clinicians

(This document is regularly updated.
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In partnership with

BIA — British Infection Association

BRITISH PHARMACOLOGICAL SOCIETY

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COVID-19 Therapeutics & Support Group partners

Royal College of Physicians Joint Specialty Committee for Infectious Disease (lead partner)
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Brighton and Sussex University Hospitals NHS Trust
Cardiff and Vale University Health Board
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Document management

This document is subject to constant review. If you identify any information that needs to be updated please contact admin.ncl-mon@nhs.uk.

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Contents

Abbreviations

Abbreviation	Meaning
CMA	Conditional Marketing Authorisation
CMO	Chief Medical Officer
CUP	Compassionate Use Programme
DHSC	Department of Health and Social Care
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
MHRA	Medicines Healthcare Products Regulatory Agency
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

- Remdesivir is approved for the treatment of COVID-19 in adults and adolescents requiring supplemental oxygen
- An interim Clinical Commissioning Policy sets out inclusion and exclusion criteria for the use of remdesivir in the UK
- There is no interaction expected between remdesivir and dexamethasone. Advice on the appropriate use of dexamethasone for COVID-19 is available at https://www.ctag-support.org.uk/immunomodulators
- Hospitals managing COVID-19 cases should make every effort to enrol COVID-19 patients in national priority clinical trials
- 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 <u>interim supporting information</u> on the appropriate use of newly licensed and 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

Remdesivir

- Preliminary results from one randomised controlled trial suggest remdesivir reduces time to recovery in hospitalised patients with confirmed SARS-CoV-2 infection and radiographic infiltrates or hypoxia[2] (see remdesivir evidence summary).[1]

- An Interim Clinical Commisioning Policy sets out inclusion and exclusion criteria for the use of remdesivir in the NHS[3,4] – **details are summarised in Section 3**
  - Enrolment into ISARIC-CCP CRF (Tier 0; no consent required) is encouraged

- A remdesivir Compassionate Use Programme (CUP) is available for children <12 years or adolescents aged 12-17 years and weighing <40 kg with severe COVID-19 – **details are summarised in Section 4**
  - CTAG encourages enrolment into ISARIC-CCP CRF (Tier 0; no consent required) as data for young children will not be available from interventional clinical trials.

- CTAG are of the opinion that patients receiving remdesivir should ideally have laboratory confirmed SARS-CoV-2 infection.[b] In the absence of a confirmed virological diagnosis, a multidisciplinary team should have a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.

- CTAG are of the opinion that remdesivir is unlikely to improve clinical outcome in people who appear clinically to be in the recovery phase of the illness, or those who have required mechanical ventilation or ECMO for a number of days and do not have ongoing evidence of high viral burden or ongoing viral replication, nor have advanced immunosuppression that may put them at risk of reactivation.

2.1.   Remdesivir is approved for the treatment of COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen

2.2.   Other antiviral medicines are being investigated for the management of COVID-19; the current evidence-base for these medicines is summarised in Appendix 1.

2.3.   Hospitals managing COVID-19 cases, including those treated with remdesivir, should make every effort to enrol COVID-19 patients in national priority clinical trials[5–7] – refer to Section 6.

2.4.   The following nationally prioritised trials for investigative antiviral medicines for hospitalised patients with COVID-19 are open to recruitment (both allow concurrent use of remdesivir):
  - RECOVERY (in hospital trial; UK study open to all Trusts)
  - REMAP-CAP (critical care trial; international with UK sites) COVID-19 antiviral and immunomodulatory domains
  - ACCORD-2 (UK Phase II clinical trials program) antiviral and immunomodulatory subprotocols

2.5.   Information for the use of dexamethasone and investigative immunomodulators for COVID-19 (e.g. tocilizumab, sarilumab, anakinra) is available at https://www.ctag-support.org.uk/immunomodulators

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[b] Benefit associated with remdesivir has been demonstrated in trials which required a recently positive PCR result for enrolment.

2.6.   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 still be permitted (**Error! Reference source not found.**)

2.7.   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 local Principal Investigator responsible for their treatment.

2.8.   CTAG are of the opinion that trials offering host directed therapy (particularly immunomodulation) should seek to ensure access to administration of licensed remdesivir where appropriate for participants within the trial.

2.9.   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/

3.   Remdesivir summary – NHS Interim Commissioning Policy

Remdesivir 100 mg concentrate for solution for infusion / Remdesivir 100 mg powder for concentrate for solution for infusion (Veklury®; conditional marketing authorisation)						
Indication[7,8,18]	Dose[4,9]	Duration[4,9]	Exclusion criteria[7,8,18]	Stopping criteria[7,8,18]	Drug specific monitoring[4,9]	Supply
As per SPC • Treatment of patients hospitalised with COVID-19 • Adults and adolescents (≥12 years with body weight ≥40 kg) • Pneumonia requiring supplemental oxygen • Use of remdesivir is confined to healthcare facilities in which patients can be monitored closely **Refer to the Interim Clinical Commisioning Policy for additional eligibility criteria during times of limited supply.**	• Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion • Day 2 onwards – 100 mg given once daily by intravenous infusion Infuse dose over 30 -120 minutes; see the SPC for the relevant product for full details, and Medusa for local variations: https://injmed.wales.nhs.uk/IVGuideDisplay.asp	The total duration of treatment should be at least 5 days and not more than 10 days	• Remdesivir should not be used in patients with eGFR < 30ml/min • Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal (ULN) at baseline	Remdesivir should be discontinued in patients who develop: • ALT ≥ 5 times the ULN during treatment. It may be restarted when the ALT is < 5 times the ULN • Or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase or INR	Limited information available, generally well tolerated. Reversible Grade 1 or 2 ALT or AST elevation observed. Daily monitoring of renal (Creatinine and Urea) and liver (ALT, AST) functions should be performed.	Refer to the Interim Clinical Commisioning Policy

4. Remdesivir summary – Gilead compassionate use programme

Remdesivir infusion (formerly GS-5734)						
Eligibility criteria[10]	Exclusion criteria[10]	Dose[11]	Duration[10]	Special precautions[11]	Drug specific monitoring[11]	Supply route[10]
Either • Children <12years of age • Adolescents aged 12-17 years and weighing <40 kg And • Hospitalization • Confirmed COVID-19 • Severe manifestation of disease	o Evidence of Multi-organ failure o Pressor requirement to maintain blood pressure o ALT levels > 5 X ULN o Creatinine Clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration o Concomitant administration of other investigational medicines for COVID-19 is not permitted while receiving remdesivir.	Infuse dose over 30 -120 minutes; see the EAMS treatment protocol for the relevant product for full details. 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.	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. Daily monitoring of renal (Creatinine and Urea) and liver (ALT, AST) functions should be performed	Requests for remdesivir for individual patient use at https://rdvcu.gilead.com/. Any communication with Gilead should include UKICOVID-19@gilead.com

5.   Prophylaxis: Supporting information

5.1.   Refer to information in 2.1 to **Error! Reference source not found.**

5.2.   The following prioritised trials for investigative antiviral medicines for the prevention of COVID-19 are open to recruitment:
   o COPCOV (healthcare workers or hospitalised patients or relatives exposed or potentially exposed or other high risk groups; international with UK sites)

6.   UK clinical studies investigating antiviral medicines

6.1.   NIHR is working with the Department of Health and Social Care (DHSC) to coordinate the national research agenda[12].

6.2.   Organisations should prioritise support for Urgent Public Health COVID-19 studies which have been nationally prioritised[12]. 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[6].

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

6.4.   Antiviral interventional studies and observational studies of relevance to COVID-19 treatment are summarised below:
   o Table 1: Active studies
   o Table 2: Closed to recruitment

6.5.   For trials investigating immunomodulatory medicines, please refer to https://www.ctag-support.org.uk/immunomodulators

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 – Azithromycin + SoC
		RECOVERY[†,‡,◊,#] (UK study, open to all Trusts; ISRCTN16912075)	First randomisation (Part A & B simultaneously): 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 **Patients receiving dexamethasone, or remdesivir (either by CMA or by CUP) are eligible for RECOVERY[13,14].**	First randomisation – Part A[§]: – SoC – Azithromycin + SoC – Low-dose corticosteroids + SoC (paediatrics only) First randomisation – Part B: – No additional treatment – Convalecent plasma Second randomisation[§] in addition to the first randomisation (refer to CTAG Immunomodulators position statement): – No additional treatment – Tocilizumab
		REMAP-CAP[†,‡,◊,#] (International study with UK sites; NCT02735707)	Critical care; adults (≥18 years) with suspected or confirmed COVID-19. **Patients receiving dexamethasone, or remdesivir (either by CMA or by CUP) are eligible for REMAP-CAP[15,16].**	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 (refer to CTAG Immunomodulators position statement).
		COPCOV[†] (UK study; NCT04303507)	– Preventative treatment for healthcare workers (≥16 years)	• Placebo • Hydroxychloroquine **MHRA have approved a request to recommence recruitment (link)**
		ACCORD-2[‡,◊,#] (UK Phase II clinical trials program)	Potentially different for each sub-protocol **Patients receiving dexamethasone or remdesivir (either by CMA or by CUP) are eligible for ACCORD-2[17,18].**	Multiple subprotocols including: • Bemcentinib + SoC vs. SoC • Heparin + SoC vs. SoC **(inactive)** Refer to CTAG Immunomodulators position statement for status of investigative immunomodulator subprotocols.

Status	Trial	Cohort	Interventions
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). § Not all paediatric age groups are eligible for all treatment arms, refer to trial protocol for arm specific eligibility criteria. ◊ Concurrent use of remdesivir is permitted. # Concurrent use of dexathasone is permitted (except with interferon arm of REMAP-CAP).

Table 2: Closed to recruitment in the UK - Antiviral interventional clinical trials

Status	Trial	Cohort	Interventions
Closed to recruitment	ACTT Stage1[†] (International study with limited UK sites; NCT04280705)	Hospital inpatients (≥18 years); adults with confirmed COVID-19 (severe disease)	(result) – 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 (result; not mechanically ventilated): – Remdesivir 5 days + SoC – Remdesivir 10 days + SoC Part B (mechanically ventilated and extension treatment groups): Remdesivir 10 days + SoC
	SNG016[†] (Phase II study, UK study with limited sites[19]; 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[20]	• Placebo + SoC • Inhaled interferon (SNG001) + SoC
	RECOVERY[†] (UK study, open to all Trusts; ISRCTN16912075)	Hospital inpatients; adults and paediatrics (any age) with suspected or confirmed COVID-19	First randomisation – Part A: • Hydroxychloroquine + SoC (result) • Lopinavir-ritonavir + SoC (result)

			• Low-dose dexamethasone (result)

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/

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.

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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).
22 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.
06 June 2020	3.0	Included unlicensed remdesivir EAMS and NHS implementation plan for that scheme; updated Section 2 accordingly and added a new monograph (Section 5). Moved studies ACTT-1, 5773, 5774 and SNG016 into a new 'Closed to recruitment' table. Updated evidence summaries in Appendix 1 (remdesivir; chloroquine/hydroxychloroquine).
12 June 2020	3.1	Updated NHS implementation plan for EAMS. Updated evidence summaries in Appendix 1 (remdesivir; chloroquine/hydroxychloroquine).
29 June 2020	3.2	Made reference to RECOVERY dexamethasone results. Added CTAG advice on the use of remdesivir. Updated arms of PRICIPLE study. Updated evidence summaries in Appendix 1 (systemic interferon; convalescent plasma).
03 July 2020	3.3	Moved ACCORD-2 to 'Active studies' table. Added discontinued arms of RECOVERY to 'Closed to recruitment' table. Updated evidence summaries in Appendix 1 (lopinavir/ritonavir).
07 July 2020	4	Updated with information on conditional marketing authorisation for remdesivir; EAMS programme lapsed so references removed
18 Aug 2020	4.1	Reformatting throughout. Updated evidence summaries in Appendix 1 (chloroquine/hydroxychloroquine, azithromycin, interferon (nebulised), convalescent plasma).

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *N Engl J Med*. Published online May 22, 2020:NEJMoa2007764. doi:10.1056/NEJMoa2007764

2. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349

3. DHSC, MHRA, NHS. CEM/CMO/2020/028(U) - Publication of an interim clinical commissioning policy: Remdesivir for patients hospitalised with COVID-19 (adults and children aged 12 years and older). Published online March 9, 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103672

4. DHSC, Scottish Government, Welsh Government, Department of Health (NI). Rapid Policy Statement: Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older). Published online March 7, 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103617

5. Atherton F, Calderwood C, McBride M, Whitty C, Powis S. CEM/CMO/2020/012 - Novel Coronavirus: Clinical Trials. https://www.cas.mhra.gov.uk/ViewAndAcknowledgment/viewAttachment.aspx?Attachment_id=103495

6. Atherton F, Smith G, McBride M, Whitty C, Powis S. CEM/CMO/2020/020 - Recruiting Patients for Clinical Trials for COVID-19 Therapeutics. https://nice.us8.list-manage.com/track/click?u=7864f766b10b8edd18f19aa56&id=230896317d&e=f70840a02d

7. Atherton F, Smith G, McBride M, Whitty C, Powis S. CEM/CMO/2020/032 - Covid-19 Research And Treatment Trials. Published August 18, 2020. https://www.cas.mhra.gov.uk/ViewAndAcknowledgment/viewAttachment.aspx?Attachment_id=103655

8. DHSC, MHRA, NHS. CEM/CMO/2020/028 -Publication of an interim clinical commissioning policy: Remdesivir for patients hospitalised with COVID-19 (adults and children aged 12 years and older). Published online June 7, 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103063

9. Gilead Sciences Ltd. Veklury 100 mg powder for concentrate for solution for infusion Summary of Product Characteristics (SmPC) - (emc). Published June 7, 2020. Accessed July 10, 2020. https://www.medicines.org.uk/emc/product/11597/smpc

10. Email communication with Gilead (Dr Shayon Shalehi). Published online April 14, 2020.

11. MHRA. EAMS 11972/0001 Remdesivir 100 mg powder for concentrate for solution for infusion. Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals. Published online May 26, 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/887275/EAMS__11972_0002__TP__HCP_Solution.pdf

12. National Institute for Health Research. NIHR's response to COVID-19. Accessed March 30, 2020. https://www.nihr.ac.uk/covid-19/

13. RECOVERY. Remdesivir and RECOVERY Statement V1.0. Published online May 27, 2020. https://www.recoverytrial.net/files/recovery-and-remdesivir-v1-0-2020-05-27-1.pdf

14. Brudlo W. Personal Communication with RECOVERY Clinical trials administrator - Dexamethasone. Published online June 19, 2020.

15. Al-Beidh F. Personal communication with UK REMAP-CAP trial manager. Published online May 28, 2020.

16. Al-Beidh F. Personal Communication with UK-REMAP-CAP trial manager for dexamethasone. Published online June 17, 2020.

17. Email communication with Professor Tom Wilkinson (PI for ACCORD-2). Published online June 4, 2020.

18. Wilkinson T. Email communication with Tom Wilkinson (PI for ACCORD-2) for Dexamethasone. Published online January 7, 2020.

19. NIHR supports COVID-19 trial looking to reduce symptoms and upregulate lung antiviral defences. Accessed April 2, 2020. https://www.nihr.ac.uk/news/nihr-supports-covid-19-trial-looking-to-reduce-symptoms-and-upregulate-lung-antiviral-defences/24484

20. Personal communication with Synairgen (Richard Marsden). Published online April 28, 2020.

21. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

22. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine*. 2020;0(0):null. doi:10.1056/NEJMoa2015301

23. Li Y, Xie Z, Lin W. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). *Cell Press*. Published online 2020. doi:10.1016/j.medj.2020.04.001

24. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. Published online March 18, 2020:NEJMoa2001282. doi:10.1056/NEJMoa2001282

25. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0

26. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. Published online May 14, 2020:m1849. doi:10.1136/bmj.m1849

27. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. Published online April 10, 2020:2020.03.22.20040758. doi:10.1101/2020.03.22.20040758

28.   Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. *medRxiv*. Published online July 15, 2020:2020.07.15.20151852. doi:10.1101/2020.07.15.20151852

29.   Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020;3(4):e208857-e208857. doi:10.1001/jamanetworkopen.2020.8857

30.   European Medicines Agency. COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine. Published online April 23, 2020. Accessed May 19, 2020. https://www.ema.europa.eu/en/documents/press-release/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine_en.pdf

31.   Lokugamage KG, Hage A, Schindewolf C, Rajsbaum R, Menachery VD. SARS-CoV-2 is sensitive to type I interferon pretreatment. Published online 2020. doi:https://doi.org/10.1101/2020.03.07.982264

32.   Hung IF-N, Lung K-C, Tso EY-K, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *The Lancet*. Published online May 2020:S0140673620310424. doi:10.1016/S0140-6736(20)31042-4

33.   Davoudi-Monfared E, Rahmani H, Khalili H, et al. *Efficacy and Safety of Interferon Beta-1a in Treatment of Severe COVID-19: A Randomized Clinical Trial*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.05.28.20116467

34.   Zheng C, Wang J, Guo H, et al. Risk-adapted Treatment Strategy For COVID-19 Patients. *International Journal of Infectious Diseases*. 2020;94:74-77. doi:10.1016/j.ijid.2020.03.047

35.   Zhou Q, Wei X-S, Xiang X, et al. Interferon-a2b treatment for COVID-19. Published online April 10, 2020. doi:10.1101/2020.04.06.20042580

36.   Djukanović R, Harrison T, Johnston SL, et al. The Effect of Inhaled IFN-β on Worsening of Asthma Symptoms Caused by Viral Infections. A Randomized Trial. *Am J Respir Crit Care Med*. 2014;190(2):145-154. doi:10.1164/rccm.201312-2235OC

37.   Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Medicine and Infectious Disease*. 2020;34:101663. doi:10.1016/j.tmaid.2020.101663

38.   Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. Published online March 20, 2020:105949. doi:10.1016/j.ijantimicag.2020.105949

39.   Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New England Journal of Medicine*. 2020;0(0):null. doi:10.1056/NEJMoa2019014

40.   Liu STH, Lin H-M, Baine I, et al. *Convalescent Plasma Treatment of Severe COVID-19: A Matched Control Study*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.05.20.20102236

41.   Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical
      Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical
      Trial. *JAMA*. Published online June 3, 2020. doi:10.1001/jama.2020.10044

42.   Gharbharan A, Jordans CCE, Geurtsvankessel C. Convalescent Plasma for COVID-19. A
      randomized clinical trial. :16.

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:
- Table 3: Benefit may exceed risk
- Table 4: Inadequate data to recommend use

Table 3: Evidence base for specific therapies for SARS-CoV-2 infection: Benefit exceeds 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.	**NICE have published rapid evidence summary for remdesivir:** **https://www.nice.org.uk/advice/es27/chapter/Key-messages** **BMJ have published a rapid evidence summary for remdesivir:** **https://www.bmj.com/content/370/bmj.m2924?utm_source=twitter&utm_medium=social&utm_term=hootsuite&utm_content=sme&utm_campaign=usage** 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[21]. 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. A preliminary report of a double-blind, randomized, controlled trial among adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement compared remdesivir to placebo[1]. Preliminary results from the 1059 patients with data available showed shorter time to recovery with remdesivir (median 11 days (95% CI 9-12) in remdesivir arm, *vs.* 15 days (13-19) in placebo arm (rate ratio for recovery 1.32; 95% CI 1.12-1.55; P<0.001). Mortality was numerically lower in the remdesivir group than in the placebo group, but the difference was not significant. Kaplan Meier 14-day mortality estimates were 7.1% with remdesivir *vs.* 11.9% with placebo (hazard ratio for death 0.70; 95% CI 0.47-1.04). Final report awaited. An open-label randomized, controlled trial of 397 hospitalized patients with SARS-CoV-2 pneumonia compared 10-day *vs.* 5-day courses of remdesivir.[22] By day 14, clinical improvement occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, there was no significant difference between 5-day and 10-day courses at day 14 (P=0.14).	No significant adverse safety signals detected in the COVID-19 RCTs[21].	Refer to the Interim Clinical Commissioning Policy and the compassionate use programme criteria at: https://rdvcu.gilead.com

Table 4. Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommend use

*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® (umifenovir) 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.[23] 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).[24(p19)] The RECOVERY randomised controlled trial issued a press release announcing closure of recruitment to the trial's lopinavir-ritonavir arm (n=1,596 *vs.* 3,376 randomised to usual care) following a data monitoring review. There was no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58). However, the investigators note that they were unable to study a large number of patients on invasive mechanical ventilation because of difficulty administering the drug to patients on ventilators. Therefore, conclusions could not be made regarding effectiveness among mechanically ventilated patients. Full results are awaited. The SOLIDARITY trial issued a press release accouncing closure of the lopinavir/ritonavir arm following review of interim results, and evidence from all trials presented at a WHO Summit. Lopinavir/ritonavir was noted to produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard care. Full results awaited.	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 in REMAP-CAP trial

Chloroquine (CQ) / Hydroxychloroquine (HCQ)

Studies perfor-med*	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*.[25] Two RCTs from China have compared HQ with SoC in hospitalised patients with mild-moderate COVID-19. The first (n=150, open-label[26]) reported no difference between arms in viral negative conversion by 28 days: 85.4% (95% CI 73.8-93.8%) vs 81.3% (71.2-89.6%). There were higher rates of adverse events (30% versus 9%) in the HCQ arm. The second, released as a preprint (n=62, blinding unclear[27]), reported faster time to clinical recovery with HCQ, defined by normalisation of body temperature (1 day quicker) and faster time to chest CT improvement (80.6% vs 54.8% at day 6). Eventual clinical outcomes are not reported. The RECOVERY RCT, a multi-arm multi-centre open-label study of hospitalised COVID-19 patients in the UK, has reported results of its HCQ arm as a preprint.[28] The authors report no significant difference between the HCQ arm (1561 patients) and the SoC arm (3155 patients) in the primary endpoint of all-cause mortality at 28 days: 26.8% mortality in the HCQ group versus 25.0% in the SoC group, RR 1.09 (95% CI 0.96-1.23). This finding is consistent in multiple pre-specified subgroup analyses including age and days since symptom onset. For secondary outcomes, HCQ was associated with a lower probability of discharge alive at 28 days (RR 0.91, 95% CI 0.85-0.99) and higher rate of progression to a composite outcome of death or invasive mechanical ventilation (RR 1.12, 95% CI 1.01-1.25). The SOLIDARITY trial issued a press release accouncing closure of the HCQ arm following review of interim results, and evidence from all trials presented at a WHO Summit. HCQ was noted to produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared SoC. Full results awaited.	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.[29] 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.[30] The RECOVERY RCT pre-print reported no significant difference in rates of new major cardiac arrythmia between patients who received HCQ and SoC, for the 44.7% & 43.0% of patients for whom this data was available in each arm.[28] Further safety data has not yet been reported.	Various licensed indications, including malaria and rheumatoid arthritis. Included in COP-COV trial (prophylaxis)

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.[31] 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.[32] 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 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 this 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. A preprint reports an open-label RCT carried out in a single centre in Iran, comparing SoC plus subcutaneous IFNβ-1a (three times per week for 2 weeks, n=42), to SoC alone (n=39).[33] SoC comprised HCQ and lopinavir/ritonavir for all patients, and antibiotics and corticosteroids in some patients. There was no difference between groups in the primary outcome of time to clinical improvement assessed on a 6 category ordinal scale. The authors report a significant difference in 28 day mortality as secondary outcome (19% in the IFNβ-1a group vs 43.6% in the SoC group), however there is a high risk of bias due to missing outcome data as multiple patients are excluded from the intervention arm because of mortality within the 1st week of treatment.	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.[34] 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.[35(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. No clinical outcomes are reported, and findings may be confounded as the study was not randomized or blinded. Furthermore, the patients 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%). The SNG016 trial, a phase II double-blind multi-centre RCT of SNG001 (a nebulized formulation of IFNβ-1a) versus placebo in hospitalized patients with COVID-19, issued a press release announcing that patients who received the drug (n=48) had a 79% lower chance of developing severe disease (defined as requiring ventilation or death) than the placebo group (n=50). They also report that patients treated with SNG001 were more likely to recover by day 28 (OR 3.86, 95% CI 1.27-11.75) as determined on an 8 point ordinal scale. The event rates in each group are not reported and overall mortality in the trial was low (3/98 patients, all in the placebo group). Publication of the full results is required for full interpretation.	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.[36]	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/).

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.[37,38] 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. A multi-centre open-label RCT in Brazil compared HCQ (n=221), to HCQ plus azithromycin (n=217), to SoC (n=227) in hospitalised patients with mild-moderate COVID-19 (maximum O2 requirement of 4L/min or FiO2 40%).[39] There were no between-group differences in the primary outcome of clinical status at day 15 (measured on a 7 point ordinal scale) or in secondary outcomes including requirement for mechanical ventilation. There was low mortality in the cohort (n=18) with no between-group differences. Higher rates of adverse events were reported in the arms containing HCQ (39.3% or 33.7%, versus 22.6%), including QTc prolongation and deranged liver function.	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.

Convalescent Plasma

Studies performed*	Data: SARS, MERS and other	Data: SARS-CoV-2	Safety profile	UK feasibility
Siv; Miv Sa; Ma Sc; Mc S2c	*In vitro* evidence demonstrates neutralisation of SARS-COV2 and MERS-CoV by specific antibodies. Animal models of SARS and MERS suggest neutralising antibodies or convalescent plasma may be efficacious for prophylaxis and/or treatment. Retrospective observational clinical studies in SARS report improvements in mortality, or time to clinical improvement, in patients treated with convalescent plasma in comparison to groups who did not receive the treatment. These studies were small, non-randomised and at risk of bias. No RCTs of convalescent plasma for treatment of SARS or MERS have been performed. A clinical trial (NCT02190799) assessing feasibility and safety of convalescent plasma treatment in MERS was initiated, but did not recruit any patients and was withdrawn. Several RCTs have been performed assessing hyperimmune plasma or immunoglobulin for treatment of severe influenza. While one small trial comparing hyperimmune IVIG with standard IVIG reported a mortality benefit in patients with pandemic H1N1 influenza, others have not replicated this benefit. A pooled meta-analysis assessed effectiveness of convalescent plasma or hyperimmune immunoglobulin in treatment of SARS or severe influenza (Mair-Jenkins et al, 2015). The authors report a pooled odds ratio of 0.25 (95% CI 0.14-0.45) for mortality, although they note that the included studies were mainly of low quality and at high risk of bias.	A preprint compared outcomes among 39 patients with severe to life-threatening COVID-19 who received convalescent plasma to a cohort of propensity score- matched controls (matching based on age, sex, comorbidities, severity, insurance, co-administered therapies)[40]. In a covariate-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19; 95% CI 0.05-0.72; p=0.015), but not for intubated patients (1.24; 0.33-4.67; p=0.752). However, this was an observational study with the potential for residual confounding; inferences are therefore limited. An open-label, multicenter, randomized clinical trial in Wuhan, China compared convalescent plasma to standard care among 103 patients with severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation) COVID-19[41]. At 28 days, there was no difference between the convalescent plasma and standard care arms in clinical improvement (51.9% vs 43.1%; hazard ratio 1.40; 95% CI 0.79-2.49; P = .26) or mortality (15.7% vs 24.0%; OR 0.65; 95% CI 0.29-1.46]; P = .30). Convalescent plasma treatment was associated with negative conversion of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR 11.39; 95% CI 3.91-33.18; P < .001). However, the trial was underpowered for clinical outcomes and median time between the onset of symptoms and randomization was 30 days, suggesting late initation of therapy. Adverse events were reported for the intervention group only (see 'Safety profile'). Furthermore, a greater proportion of participants in the treatment group received co-interventions, compared to the control group, which may have been influenced by knowledge of allocation. A preprint of an open-label randomized trial comparing convalescent plasma with standard of care therapy in patients hospitalized for COVID-19 in the Netherlands reported that the trial was stopped early (n=86 enrolled) as 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.[42] At the time of cessation, the adjusted odds ratio for overall mortality for patients treated with convalescent plasma was 0.95 (CI 0.20 – 4.67; p=0.95) and for improvement in the WHO COVID-19 disease severity score on day 15 was 1.30 (CI 0.52 - 3.32).	Transfusion-related adverse events well-recognised. 2/52 patients who received convalescent plasma in the RCT from China[41] experienced transfusion-associated adverse events; both improved with supportive care.	Included as an arm in the UK RECOVERY trial.

References for 'Data: SARS, MERS and other'

Al Ghamdi M, Al Ghamdi KM, Ghandoora 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, Y. et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus 4, 709 (2015).

Arabi YM, Alothman 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-β1b (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.

Beigel, J. H. et al. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. The Lancet Respiratory Medicine 7, 941–950 (2019).

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-β1b 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.

Cheng, Y. et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 24, 44–46 (2005).

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.

Davey, R. T. et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. The Lancet Respiratory Medicine 7, 951–963 (2019).

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-α2b 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]

Hung, I. F. N. et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 144, 464–473 (2013).

Jiang, L. et al. Potent neutralization of MERS-CoV by human neutralizing monoclonal antibodies to the viral spike glycoprotein. Sci Transl Med 6, 234ra59 (2014).

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.

Mair-Jenkins, J. et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J. Infect. Dis. 211, 80–90 (2015).

Meulen, J. ter et al. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. The Lancet 363, 2139–2141 (2004).

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.

Roberts, A. et al. Therapy with a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody reduces disease severity and viral burden in golden Syrian hamsters. J. Infect. Dis. 193, 685–692 (2006).

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 yand safety of hydoxychlorquine (HCQ) in the treatment of patients with common coronavirus disease-19 (COVID-19). Journal of Zheijang University. 2020 Mar.

Soo, Y. O. Y. *et al.* Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin. Microbiol. Infect.* **10**, 676–678 (2004).

Subbarao, K. et al. Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. J. Virol. 78, 3572–3577 (2004).

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].

Traggiai, E. *et al.* An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nat. Med.* **10**, 871–875 (2004).

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.Ying, T. *et al.* Exceptionally Potent Neutralization of Middle East Respiratory Syndrome Coronavirus by Human Monoclonal Antibodies. *J Virol* **88**, 7796–7805 (2014).

Zhao, J. et al. Passive immunotherapy with dromedary immune serum in an experimental animal model for Middle East respiratory syndrome coronavirus infection. J. Virol. 89, 6117–6120 (2015).

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],

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