Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19).

Version 3.0: *Guidance in this document is based on the latest available evidence on 19 April 2020. If using a printed copy the information is valid only on the day of printing. The document is subject to change in response to emerging new evidence; for the most recent version of the document please check:*

https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/ *a*nd
https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/guidanceforhealthcareworkers/

Scope

This document is intended for use by healthcare professionals. The guidance is specific to the management of acute respiratory infection in adults when SARS-CoV-2 COVID-19 infection is confirmed. While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

The use of investigational or off-label medicinal products to treat patients with confirmed COVID 19 is at an experimental stage. The evidence of clinical efficacy is lacking. Patients (or their next of kin, by phone) should be adequately informed about the uncertain efficacy, and respective toxicities of the agents, and their consent obtained.

Comprehensive information for members of the public and healthcare professional on the prevention, diagnosis and management COVID-19 is available from the following sources:

- HSE Guidance for Paediatrics is available at: https://hse.drsteevenslibrary.ie/Covid19V2/paediatrics#link%20to%20start%20of%20Interim%20guidelines038
- Department of Health: https://www.gov.ie/en/publication/472f64-covid-19-coronavirus-guidance-and-advice/#treatment
- European Centre for Disease Prevention and Control: https://www.ecdc.europa.eu/en/novel-coronavirus-china
- Health Service Executive (HSE): https://www2.hse.ie/conditions/coronavirus/coronavirus.html#Treatment
- HSE Health Protection Surveillance Centre (HPSC): https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/
- World Health Organisation:
    - https://www.who.int/health-topics/coronavirus
    - https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

Key Changes to Version 3 of *Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19)* are highlighted within the text.

Major Changes:

1. **Azithromycin has been removed as an agent of choice from the guideline due to its lack of proven clinical efficacy and safety concerns in COVID 19, thus its use in combination with hydroxychloroquine is not recommended in the context of COVID 19**
2. **Additional criteria must be satisfied prior to the prescribing of an investigational agent – see Table 2**

Specific Antiviral Therapy in SARS-CoV-2 (COVID-19)

The guidance in this document is informed by rapid evidence reviews completed by the COVID-19 Evidence Review Group formed by the NCPE/MMP/NMIC. The evidence reviews are updated weekly and are available at the following link:
https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/

Participation in clinical trials is strongly recommended. Multiple agents have theoretical value in the management of COVID-19; however, actual clinical trial data that establish true efficacy are lacking. Information on on-going clinical trials, including those recruiting, is available on www.clinicaltrials.gov. There are several national bodies that can provide trustworthy information on the regulatory and ethics approvals obtained for clinical trials including the Office for National Research Ethics Committees (nationaloffice@nrec.ie).

As stated already there is a paucity of clinical evidence for any disease-specific treatment; guidance is on the best available evidence. There is a number of medicinal products under investigation for the management of COVID-19 and may be considered in severely ill patients or those at risk of severe disease. There are no comparative studies between different treatments; access to individual medicinal products may need consideration in the treatment selection process. See **Tables 3-5** for information on medicinal products.

Refer to **Table 1** for guidance on the diagnosis and treatment of respiratory tract infection in patients presenting with suspected or confirmed COVID-19.

Table 2 lists criteria for specific antiviral therapy for SARS-CoV-2 (COVID-19). Clinical judgment will be required for all cases; specialist consultation with local Infectious Disease and Microbiology teams is recommended for those cases not meeting criteria listed in **Table 2**. At present, prescribing of antivirals for the management of patients with confirmed COVID-19 disease should be **restricted to hospitals only**. Refer to Tables 3, 4, and 5 for further information on individual medicinal products. There are no medicinal products licensed and there is a paucity of clinical evidence for the disease-specific management of COVID-19.

TABLE 1 DIFFERENTIAL DIAGNOSES OF RESPIRATORY INFECTIONS IN PRESENTATION OF SUSPECTED CASE OF COVID-19 (adapted from St James's Hospital Protocol)

	Investigations	**Treatment**
Community Acquired Pneumonia	- Arterial blood gases - Chest X-ray - Full Blood Count - Urea and electrolytes - Blood cultures - Sputum cultures - Urine for Legionella antigen and Pneumococcal antigen	Treat according to local antimicrobial prescribing policy.
Healthcare Associated Pneumonia	- Arterial blood gases - Chest X-ray - Full Blood Count - Urea and electrolytes - Blood cultures - Sputum cultures - 12 lead ECG	Treat according to local antimicrobial prescribing policy.
Acute Infective Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)	- Arterial blood gases - Chest X-ray - Full Blood Count - Urea and electrolytes - Blood cultures - Sputum cultures - 12 lead ECG - Pulmonary Function Tests	Treat according to local antimicrobial prescribing policy.
Viral Respiratory Infection	- Arterial blood gases - Chest X-ray - Full Blood Count - Urea and electrolytes - Blood cultures - Sputum cultures - Nasopharyngeal aspirate	Treat according to local antimicrobial prescribing policy. **AND** If influenza, the national *Guidance on the use of antiviral agents for the treatment and prophylaxis of influenza (2019-2020)* available from: https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/guidance/antiviraltreatmentandprophylaxisguidance/Antivirals%20guidance%20for%20treatment%20and%20prophylaxis%20of%20influenza.pdf
Suspected Covid-19 Infection	- Test as per most recent guidance from HPSC.	See **Table 2.**

Table 2. Criteria and Potential Antiviral Therapy in ADULTS with Confirmed COVID-19# (*Clinical trials in Ireland, an evolving situation, see page 2 for comment)		
Disease Category - defined by COVID Respiratory Scale (CRS) as per ITS irishthoracicsociety.com	**Criteria**	**Potential Antiviral Treatment**
CRS A	SaO2>94%, RR<20 No O2 requirement or nasal cannula </= 3L	No antiviral
CRS B, C1,C2	Hospitalised with confirmed COVID-19 AND SaO2<94%, RR>20 B: nasal cannula >3L/min or venturi 24-60% C1: High flow nasal O2 (HFNO) (AIRVO) (poor response to venturi) C2: Non-invasive ventilation (poor response to venturi)	Clinical trial* **OR** If an investigational agent is considered outside of a clinical trial, this should be done on a case by case basis, in patients whose clinical condition is sufficiently severe to warrant investigational therapy, including: • Shared decision making, with patient informed of possible benefits and side effects • Collection of clinical outcome data, following guidance from COVID-19 core outcome sets (e.g. WHO Core Outcome Set, Appendix 3) • Assessment of the patient as per guidance from the Irish Cardiac Society regarding long QT syndrome in Appendix 4 Investigational agents: Hydroxychloroquine (HCQ) oral: see Table 4. European Medicines Agency recommend HCQ preferably be used in context of clinical trial, otherwise in accordance with national protocol. If hydroxychloroquine unavailable or contraindicated consider: Lopinavir/ritonavir (oral): see Table 5. Treatment should be initiated promptly and within 12 days following symptom onset. For patients with severe disease and suspected hyperinflammation, see HSE interim guidance for the use of tocilizumab in the management of patients with severe COVID-19; available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/
CRS D	Hospitalised with confirmed COVID-19 AND SaO2<94%, RR>20 and poor response to HFNO/ NIV ICU +/- intubation	Clinical trial* **OR** Remdesivir (intravenous): see **Table 5.** **OR** If remdesivir is unavailable treat as for CRS B, C1, C2 For patients with severe disease and suspected hyperinflammation, see HSE interim guidance for the use of tocilizumab in the management of patients with severe COVID-19; available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/

#Consultant-only decision.

Drug-Drug Interactions

Clinically significant drug-drug interactions may occur with the medicinal products used to treat COVID-19. A thorough medication history (including alternative and herbal medicines) should be obtained prior to initiation of treatment. Refer to the Summary of Product Characteristics and drug-drug interaction databases (e.g. Stockley's Interaction Checker) to check for drug-drug interactions. The University of Liverpool have developed an online database for checking drug-drug interactions with the experimental COVID-19 specific medicinal products; available online at www.covid19-druginteractions.org . Credible meds have developed a resource, that may be of use, available at www.medsafetyscan.org . Each patient's clinical risk factors and their medicines are input online. The program reports if any of the medicines are on the QTdrugs lists and calculates the patient's QTscore for risk of QT prolongation and torsades. The drugs entered will also be screened for major drug-drug interactions and contraindicated drug pairs. The resource can be used without inputting a patient identifier and there is no requirement to save the inputted data.

Dose Adjustments

Where a dose reduction is recommended in hepatic or renal impairment it is recommended to prescribe the upper end of the dose range in the context of acute respiratory infection with SARS-CoV-2 (COVID-19) to avoid under dosing. Other factors that may alter pharmacokinetics or increase the risk adverse drugs reactions (e.g. advanced age, low body weight, frailty) should also be considered in treatment and dosage decision making.

Administration of Medicinal Products in the Treatment of COVID-19

Timely initiation of medicinal products used for the treatment of COVID-19, at the recommended dose and frequency, is recommended to maximise efficacy, or the development of viral resistance. Delayed or omitted doses should be avoided, unless on the advice of the treating physician. For patients with swallowing difficulties, the University of Liverpool have developed a resource providing recommendations for the administration of medicines used in the management of COVID-19; available online at: https://liverpool-covid19.s3.eu-west-2.amazonaws.com/landing-page/Covid__Swallowing_2020_Mar13.pdf .

Pregnancy: see **Appendix 1**.

Table 3 Hydroxychloroquine (HCQ) for the treatment for COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.							
Drug Hydroxychloroquine (HCQ)	**Proposed MOA in COVID-19**	**Contra-indications**	**Monitoring**	**Renal/Hepatic Impairment**	**Side-Effects**	**Drug-Drug Interactions**	**Preparation & Sourcing**
Unlicensed indication, included from expert consensus. **Recommended Dose:** Day 1: 400mg TWICE a day; Days 2-5 200mg TWICE a day (total duration 5 days*). *While there are different doses and duration of treatments recommended in various national and specialty guidelines, given the lack of robust evidence and to minimise adverse events a duration of 5 days is recommended.	Reported to have anti-SARS-CoV activity *in vitro* suggesting potential pharmacological agent for the treatment of COVID-19 infection. *In vitro* study reported more potent inhibition of SARS-CoV-2 with HCQ compared to chloroquine. Small clinical studies have shown no robust evidence of efficacy against SARS-CoV-2. Large clinical trials are ongoing.	Hypersensitivity to active ingredients or any of the excipients. Known hypersensitivity to 4-aminoquinoline compounds i.e. hydroxychloroquine, chloroquine and others. Pre-existing maculopathy of the eye Children aged <6 years of age (200mg tablets not adapted for weight <35kg). *Contd. next page*	**Full Blood Count:** Myelosuppression may occur rarely; monitor if pre-existing myelosuppression or if receiving other myelosuppressive agents concomitantly. **ECG:** QTc prolongation including Torsades de Pointe have been reported and may occur. Use with caution if pre-existing QTc prolongation and/or known risk factors for prolongation of the QTc interval (including concomitant administration of other QTc prolonging agents). Consult appendix 4. **Blood glucose**: may cause hypoglycaemia. **Epilepsy:** may lower seizure threshold. *Contd. next page*	**Renal Impairment:** Following careful consideration the review committee advise that routine dose reduction in renal impairment may not be necessary but monitoring of renal function is warranted and consideration is advised on a case by case basis. **Hepatic Impairment:** No specific dose adjustments recommended – use with caution.	See Summary of Product Characteristics (SmPC) for full list of side-effects; available from: https://www.medicines.ie/medicines/plaquenil-tablets-33380/smpc Hydroxychloroquine is highly toxic in overdose and children are particularly susceptible to toxic side effects.	*This list is not exhaustive. Refer to SmPC and drug-drug interaction databases e.g. Stockley's and University of Liverpool online (http://www.covid19-druginteractions.org/).* Caution with concomitant QTc prolonging agents. Combination of azithromycin + HCQ is not recommended due to risk of QTc prolongation, and lack of evidence on clinical efficacy. Possible potentiation of neuromuscular blockade with aminoglycoside antibiotics. Antacids (aluminium, magnesium, and calcium salt) and adsorbents (e.g. kaolin) may reduce absorption of chloroquine; separate administration by at **least 4 hours** Avoid concomitant use of HCQ with drugs known to induce retinal toxicity. *Contd. next page*	Available as Plaquenil® (Sanofi-Aventis) from UniPhar. Currently supply of Plaquenil specifically for COVID-19 only available for hospitals. The tablets can be crushed and dispersed in water for administration.

Table 3 (continued from previous page) Hydroxychloroquine (HCQ) for the treatment for COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.							
Drug Hydroxychloroquine (HCQ)	**Proposed MOA in COVID-19**	**Contra-indications**	**Monitoring**	**Renal/Hepatic Impairment**	**Side-Effects**	**Drug-Drug Interactions**	**Preparation & Sourcing**
		Contd. Lapp lactase deficiency or glucose-galactose malabsorption. **Pregnancy** is listed a contraindication on the Plaquenil® Summary of Product Characteristics; there is evidence of safe use of HCQ in pregnancy – see **Appendix 1** for further information on use in pregnancy.	*Contd.* **G6PD:** Caution advised in patient with G6PD deficiency, may be risk of haemolysis. If status unknown, do not delay initiation of treatment in the context of moderate or severe COVID-19. **Retinal toxicity:** Due to low risk with recommended dose and duration of treatment, ophthalmological examination not required in context of COVID-19 infection. **LFTs:** abnormal LFTs have been reported (uncommon).			*Contd.* Caution if co-administering medicines which may cause adverse ocular or skin reactions HCQ may increase levels of ciclosporin and digoxin (monitor levels) Caution with anti-convulsants; HCQ may lower seizure threshold	

Table 4 Lopinavir/ritonavir for the treatment for COVID-19 (adapted from St James's Hospital Protocol). See Summary of Product Characteristics (SmPC) for full prescribing information.							
Drug **Lopinavir/ritonavir**	**Proposed MOA in COVID-19**	**Contra-indications**	**Monitoring**	**Renal/Hepatic Impairment**	**Side-Effects**	**Drug-Drug interactions**	**Preparation & Sourcing**
Unlicensed indication, included from expert consensus **Recommended Dose:** lopinavir/ritonavir 400mg/100mg TWICE a day administered as: **200mg/50mg Tablets: TWO** tablets TWICE a day (with or without food). **OR 80mg/20mg per mL Oral Solution:** 5mL TWICE a day (with food). **Duration:** 14 days	Lopinavir/ritonavir initially hypothesised to inhibit 3-chymotrypsin-like protease of SARS and MERS. This combined agent has in vitro activity against SARS-CoV and appears to have some activity against MERS-CoV in animal studies. Its use for treatment of COVID-19 has been described in case reports but there is no robust evidence to determine its effectiveness against SARS-CoV2. Large clinical trials ongoing.	Hypersensitivity to active ingredients or any of the excipients. Severe hepatic insufficiency. Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. *Contd. next page.*	**Liver Function Tests (LFTs):** deranged liver function tests and hepatic dysfunction have been reported; monitor LFTs before and during treatment. Consult appendix 4 for advice on cardiac monitoring	**Renal Impairment:** negligible renal clearance and increased plasma concentrations are not expected in renal impairment. Lopinavir and ritonavir are highly protein-bound; unlikely to be significantly removed by haemodialysis or peritoneal dialysis. *Contd. next page.*	See Summary of Product Characteristics (SmPC) for full list of side-effects; available from: https://www.medicines.ie/medicines/kaletra-200-mg-50-mg-film-coated-tablets-32560/smpc.	*Refer to SmPC and drug-drug interaction databases e.g. Stockley's and University of Liverpool online (http://www.covid19-druginteractions.org/)* Lopinavir and ritonavir are both inhibitors of cytochrome P450 enzyme isoform CYP3A. Co-administration of medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse reactions (see also contraindications). *Contd. next page*	Available as oral formulations only (tablets and oral solution). Ordering: Contact wholesaler and specific form to be completed by hospital pharmacy department. Crushing tablets significantly reduces exposure of both lopinavir and ritonavir; ↓AUC by 45% and 47% respectively (range 5-75%). Reduction variable between individuals and unpredictable. Avoid crushing tablets, if possible. See Appendix 2. *Contd. next page*

Table 4 (continued from previous page) Lopinavir/ritonavir for the treatment for COVID-19 (adapted from St James's Hospital Protocol). See Summary of Product Characteristics (SmPC) for full prescribing information.							
Drug **Lopinavir/ritonavir**	**Proposed MOA in COVID-19**	**Contra-indications**	**Monitoring**	**Renal/Hepatic Impairment**	**Side-Effects**	**Drug-Drug interactions**	**Preparation & Sourcing**
		Contd. Kaletra® oral solution contains propylene glycol and 42% v/v alcohol; contraindicated in children <14 days, pregnant women, patients with hepatic or renal failure and patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol.		*Contd.* **Hepatic Impairment:** Possible increased exposure in mild or moderate impairment; not expected to be clinically significant. Avoid in severe hepatic impairment.		*Contd.* Clinically significant drug-drug interactions are extensive. A thorough medication history (including alternative and herbal medicines) should be obtained prior to initiation of treatment.	*Contd.* Oral solution is preferable in patients unable to swallow solid dosage forms. Enteral tubes: to prevent precipitation do not dilute soln. Rinse tube with water. Oral solution incompatible with polyurethane feeding tubes. Compatible with: polyvinyl chloride (PVC) and silicone feeding tubes.

Table 5 Remdesivir for the treatment of COVID-19		
Drug – Remdesivir	**Proposed MOA in COVID-19**	**Key Information**
Unlicensed medicinal product. **Recommended Dose (as intravenous infusion):** Day 1: 200mg; Day 2-10: 100mg Refer to the manufacturer's information for reconstitution and administration details. **NOTE:** Available in two formulations, solution for injection (requires storage in freezer) and a lyophilised version (does not require storage in freezer). Follow manufacturer's storage instructions.	Remdesivir (GS-5734) is a phosphoramidate prodrug of an adenine derivative with a chemical structure similar to tenofovir alafenamide. Broad-spectrum activities against RNA viruses such as MERS and SARS in vitro in cell cultures and animal models, and has been tested in a clinical trial for Ebola. Use has been reported in COVID-19 case series. Large clinical trials are ongoing.	- Remdesivir is an investigational medicinal product only available as part of a clinical trial or on a compassionate use or via expanded access direct from the manufacturer (Gilead). European Medicines Agency conditions of use available at: https://www.ema.europa.eu/en/documents/other/conditions-use-conditions-distribution-patients-targeted-conditions-safety-monitoring-adressed_en-2.pdf - The expanded access programme is only operational at two sites in Ireland, and access is only via these two sites. - For compassionate use: Requests for the supply of this medicine must be submitted by the treating physician on an individual patient basis via the online portal: https://rdvcu.gilead.com/ . As of 25/03/2020 Gilead have confirmed that the portal is closed now for all new requests except for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease. - Email both the following addresses when an application is submitted and in all communications to help expedite the process: o Gilead UK Med Info; email: UKMed.Info@gilead.com o UKICOVID-19; email UKICOVID-19@gilead.com - In order to access remdesivir a number of documents must be completed and returned to the manufacturer; documents are provided by the manufacturer in response to a request. Steps which can be taken in advance: 1. Completion of a signed confidentiality agreement : CDA RDV CoV_Template_24Jar 2. Hospital CEO/Ethics Committee approval to allow the use of a Compassionate Access Drug in your institution (an email will suffice) - The final element of the paperwork of an application is the completion of a Prescriber Agreement - this cannot be completed in advance as it relates to the specific patient you have requested drug for. Once clinical approval is given for a patient, the Clinical Operations team will look for each of the above agreements - by having them prepared in advance (with the exception of the Prescriber Agreement) it should help expedite the process. - The clinical criteria to access remdesivir are subject to change at the discretion of the manufacturer. - Consult the product information supplied by the manufacturer for prescribing information.

References

1. Medicine.ie (2020). *Plaquenil 200mg Film-coated Tablets – Summary of Product Characteristics.* Available at: https://www.medicines.ie/medicines/plaquenil-tablets-33380/smpc [Accessed 11 Mar 2020].
2. Medicine.ie (2020). *Kaletra (80mg+20mg)/ml oral solution – Summary of Product Characteristics.* Available at: https://www.medicines.ie/medicines/kaletra-oral-solution-32561/smpc [Accessed 10 Mar 2020].
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11. Credible Meds – Med safety scan. Available online at: https://medsafetyscan.org/ [Accessed 22 April 2020].
12. Australian Don't Rush to Crush Handbook, 2nd edn SHPA (2016) Lopinavir with Ritonavir (Kaletra) monograph

Appendix 1: Pregnancy

Based on the limited available evidence, the clinical characteristics of COVID-19 pneumonia are similar for pregnant and non-pregnant adult patients of similar age.[1,2,3] At present, the approach to prevention, evaluation, diagnosis, and treatment of pregnant women with suspected COVID-19 should be similar to that in non-pregnant individuals. Consideration of the safety of all medicinal products used during pregnancy, including for the management of COVID-19, is essential**. Antivirals should only be used in a pregnant patient if the potential risk of maternal infection with COVID-19 is considered to be greater than any potential risks to the foetus from the drug. Pharmacological treatment of COVID-19 in pregnant patients should not be withheld if clinically indicated. The liquid formulation of lopinavir/ritonavir (Kaletra®) is contraindicated in pregnancy due to propylene glycol and high alcohol content; seek Pharmacy advice on available formulations and appropriateness for pregnancy. Treatment should only** be initiated with multidisciplinary input from relevant Specialities, including Infectious Diseases / Microbiology / Obstetrics / Respiratory Physicians, with the knowledge that there is no proven therapy in pregnancy and taking cognisance of additional pre-prescribing guidance in Table 2. Seek pharmacy advice on available products, choice of agent, and potential drug-drug interactions.

There is additional information on COVID-19 in pregnancy available from HPSC: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/

Evidence for Safety in Pregnancy: Antivirals used in COVID-19

Hydroxychloroquine (HCQ) in Pregnancy

The limited published data relating to the use of HCQ during human pregnancy do not indicate that the drug poses a significant risk to the foetus. However, available data primarily relate to its use at lower doses for malaria prophylaxis.[4,5] While there are concerns that use of higher doses for prolonged periods may represent an increased foetal risk, the magnitude or nature of this risk is unknown.[6] Higher doses of HCQ, similar to those recommended for the treatment of COVID-19, have been safely used during pregnancy in the context of autoimmune conditions such as systemic lupus erythematosus (SLE)[4] and international consensus guidelines on the management of SLE advocate for the continued use of HCQ throughout pregnancy.[7]

Based on available evidence, where HCQ is clinically indicated it should not be withheld in pregnant patients if the potential risks of maternal infection with COVID-19 are considered to be greater than any potential risks to the foetus from the drug.

Lopinavir/ritonavir (LPV/RTV) in Pregnancy

Based on limited available data in humans, treatment with LPV/RTV does not appear to increase the risk of adverse pregnancy outcomes.[4,5] Due to the reported association between protease inhibitors and diabetes mellitus, there may be an increased risk of new-onset diabetes, exacerbation of pre-existing diabetes, and hyperglycaemia in patients receiving protease inhibitor therapy. Pregnant women being treated with LPV/RTV should therefore be monitored for hyperglycemia.[5] **In the context of the management of Human Immunodeficiency Virus (HIV), the US Public Health Service Task Force suggest dosing of LPV/RTV may need to be altered due to pharmacokinetic changes in pregnancy. The collected data suggested the dose of LPV/RTV may need to be increased in the second and third trimesters of pregnancy, especially in protease inhibitor-experienced patients. Seek expert advice for dosing recommendations in pregnancy.**

Based on available evidence, where LPV/RTV is clinically indicated it should not be withheld in pregnant patients if the potential risks of maternal infection with COVID-19 are considered to be greater than any potential risks to the foetus from the drug. Monitor blood glucose. The tablet formulation should be used if indicated; the liquid formulation of LPV/RTV (Kaletra®) is contraindicated in pregnancy due to propylene glycol and high alcohol content.

Pregnancy References

1. The World Health Organisation. Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (nCoV) Infection is Suspected. Available online at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected [accessed on 21 Mar 2020).
2. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Chen, Huijun et al. The Lancet, Volume 395, Issue 10226, 809 – 815
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Appendix 2: Preparation of a solution from lopinavir/ritonavir tablets in the event the suspension is unavailable or contraindicated (Source: AbbVie)

AQUEOUS SUSPENSION PREPARATION (TABLET)

Oral Solution

The Kaletra/Aluvia (lopinavir/ritonavir) oral solution should be used as a first option for feeding tube administration, where available.

Because Kaletra/Aluvia oral solution contains ethanol and propylene glycol, it is not recommended for use with polyurethane feeding tubes due to potential incompatibility (Kaletra US package insert). Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used for administration of Kaletra/Aluvia oral solution. Follow instructions for use of the feeding tube to administer the medicine. Kaletra/Aluvia oral solution must be taken with food.

Tablet Formulation

The Kaletra/Aluvia tablet should not be used for feeding tube administration except when no other options exist. Kaletra/Aluvia tablets should not be chewed, broken, or crushed (Kaletra US package insert), but in a case where a patient requires feeding tube administration, the following procedures may be considered:

Please note that this method of administration has not been fully evaluated. Pharmacokinetic studies evaluating exposures of lopinavir and ritonavir are not available. Bioequivalence of a suspension prepared from the tablet to whole, intact tablets or Kaletra/Aluvia oral solution is not available.

- To prepare a suspension for feeding tube administration, full intact tablets of the appropriate dose (eg, 2 x 200mg/50mg tablets for a 400mg/100mg dose) should be dissolved in a sufficient volume of drinking water (at least 10 mL per tablet; 2 tablets in at least 20 mL water) at room temperature until completely dissolved. No agitation or stirring is needed. Dissolution of the Kaletra/Aluvia tablets will take several hours (at least 4 hours). It is recommended to initiate preparation of the suspension 6 to 12 hours in advance of administration.
- Kaletra/Aluvia tablet suspension is not suitable for long-term storage. The suspension must be used within 24 hours of preparation.
- **Do not crush or grind the tablet prior to mixing with water.** This can lead to significant drug agglomeration, drug losses due to adherence to contact surfaces, and ultimately, significantly reduced bioavailability.
- Following slow, full dissolution, the milky suspension should be carefully stirred or swirled, and then the entire volume of the resultant milky suspension may then be administered via a feeding tube as a whole dose (partial dosing less than that of the original tablet should not be attempted). A water rinse may be necessary to assure complete dosing.
- Follow instructions for use of the feeding tube to administer the medicine.

The data that supports this procedure is based on internal experiments (Data on file, M13-979).

Appendix 3: A Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection *(unpublished recommendations from the WHO Working Group on the Clinical Characterization of COVID-19 infection,* http://www.comet-initiative.org/Studies/Details/1538*)*

Domain	Measure
Viral burden	COVID-19 semiquantitative viral RNA measured by qPCR cycle threshold (Ct) in nasopharyngeal or throat swab, sputun, or upper of lower repiratory secretions
Survival	All-cause mortality at hospital discharge or 60 days
Clinical progression	WHO Clinical Progression Scale, measured daily over course of study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Notes.

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO_2 not available, use SpO_2/FIO_2 ratio with a cutoff of 200 [18]

Appendix 4: Irish Cardiac Society Clinical Guidance for COVID-19 therapies and patients with Long QT syndrome. Available at: wwwirishcardiacsociety.com in the COVID 19 information hub

Irish Cardiac Society
17 – 19 Rathmines Road Lower, Dublin 6
www.irishcardiacsociety.com

Overview of Clinical Guidance for Covid-19 therapies and patients with Long QT syndrome.

Consensus opinion document, prepared with reference to www.crediblemeds.org and guidance published in Mayo Clinic Proceedings 25th March 2020 (Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19 [published online ahead of print March 25, 2020]. *Mayo Clin Proc*. https://doi.org/10.1016/j.mayocp.2020.03.024.)

General comments:

1. Currently no robust evidence for efficacy of medicines proposed for off-label use in treatment of Covid-19 related acute respiratory distress syndrome (eg Hydroxychloroquine, Azithromycin).
2. Most if not all proposed medications (Hydroxychloroquine, Azithromycin, Kaletra (lopinavir/ritonavir)), have been shown to prolong the QT interval and/or cause Torsades de Pointes (TdeP) cardiac arrhythmia.
3. This guideline is prepared to assist decision-makers, but should never replace clinical judgement – interpretation must be individualised to each patient's risk:benefit assessment, and may alter over the course of a patient's clinical journey.
4. Persistent pyrexia and electrolyte disturbance may significantly increase risk of life-threatening arrhythmia in LQTS, so check for and manage aggressively.
5. If patient has evidence of Covid-19 associated myocarditis (eg very high Troponin and LV systolic impairment) risk of arrhythmia may be significantly increased.
6. Caution should be taken prescribing any QT prolonging medications to all patients with congenital LQTS or to patients without Congenital LQTS who are being treated for COVID19 with the QT prolonging medications mentioned. A full list of QT prolonging medications is available at the following website; www.crediblemeds.org

If patient with potential for QT prolongation is being considered for prescription of one of the off-label treatments, we recommend the following:

1. Obtain a baseline pre-treatment QTc measurement (12 lead ECG, ideally leads II or V5, correction via www.mdcalc.com/corrected-qt-interval-qtc (using HR) or http://www.medcalc.com/qtc.html using R-R interval (for patients with QRS prolongation, correct the measured QT for QRS of 100 msec before calculating). Telemetry strips etc can be used to calculate QTc to avoid recording ECGs repeatedly.
    a. If QTc < 480 msec (adult female), < 470 msec (adult male) or < 460 msec (pre-pubertal patient), then 'green light' (low-risk of TdeP) for treatment if considered clinically indicated.
    b. If QTc > 500 msec, seek modifiable factors (eg electrolyte disturbance, co-prescription of other QT prolonging mediations) and review. Considered 'red-light' (high risk of TdeP). If treatment still considered necessary arrangement for cardiac rhythm monitoring and management of resultant arrhythmia to be agreed.
    c. If QTc < 500 but above the low-risk thresholds then 'orange light' intermediate risk, proceed with caution.
2. On-treatment QTc measurements should be made at 2-4hrs post first dose (red-light patients) and 48 hrs and 96 hrs post first dose (all patients). If QTc increases by 60msec review ongoing benefit:risk ratio and review other modifiable factors as above.
3. In all potentially at-risk patients ideally use single agent as first line treatment.

Drs D Ward, J Galvin, A Brown, J Crowley and Prof D Keane, on behalf of Irish Cardiac Society (07/04/2020)
Queries to bdalton@irishheart.ie