
Version 2.0: Guidance in this document is based on the latest available evidence on 27 March 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:

Scope

This document is intended for use by healthcare professionals. The guidance is specific to the management of acute respiratory infection 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:

- 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

Key Changes to Version 2 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.

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Protocol Code: COVID19
Approved by: Dr Vida Hamilton, HSE National Clinical Advisor and Group Lead, Acute Hospitals
Contributors: Prof C Bergin, M Philbin, P Gilvarry, M O’Connor, F King, R Adams, E Fogarty, Prof D Murphy, Prof P Murray, Dr P McKenna, Dr E Breslin, B Cleary, Dr N Maher, F OShaughnessy, Dr J Donnelly

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

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 3-6 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, 5 and 6 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)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Acquired Pneumonia</td>
<td>- Arterial blood gases&lt;br&gt;- Chest X-ray&lt;br&gt;- Full Blood Count&lt;br&gt;- Urea and electrolytes&lt;br&gt;- Blood cultures&lt;br&gt;- Sputum cultures&lt;br&gt;- Urine for Legionella antigen and Pneumococcal antigen</td>
<td>Treat according to local antimicrobial prescribing policy.</td>
</tr>
<tr>
<td>Healthcare Associated Pneumonia</td>
<td>- Arterial blood gases&lt;br&gt;- Chest X-ray&lt;br&gt;- Full Blood Count&lt;br&gt;- Urea and electrolytes&lt;br&gt;- Blood cultures&lt;br&gt;- Sputum cultures&lt;br&gt;- 12 lead ECG</td>
<td>Treat according to local antimicrobial prescribing policy.</td>
</tr>
<tr>
<td>Acute Infective Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>- Arterial blood gases&lt;br&gt;- Chest X-ray&lt;br&gt;- Full Blood Count&lt;br&gt;- Urea and electrolytes&lt;br&gt;- Blood cultures&lt;br&gt;- Sputum cultures&lt;br&gt;- 12 lead ECG&lt;br&gt;- Pulmonary Function Tests</td>
<td>Treat according to local antimicrobial prescribing policy.</td>
</tr>
<tr>
<td>Viral Respiratory Infection</td>
<td>- Arterial blood gases&lt;br&gt;- Chest X-ray&lt;br&gt;- Full Blood Count&lt;br&gt;- Urea and electrolytes&lt;br&gt;- Blood cultures&lt;br&gt;- Sputum cultures&lt;br&gt;- Nasopharyngeal aspirate</td>
<td>Treat according to local antimicrobial prescribing policy.</td>
</tr>
<tr>
<td>Suspected Covid-19 Infection</td>
<td>- Test as per most recent guidance from HPSC.</td>
<td>See Table 2.</td>
</tr>
</tbody>
</table>

**AND**


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### Table 2. Criteria and Potential Antiviral Therapy in Patients with Confirmed COVID-19 (* As of 27/03/20 no active clinical trials in Ireland, an evolving situation*)

<table>
<thead>
<tr>
<th>Disease Category - defined by COVID Respiratory Scale (CRS) as per Irish Thoracic Society <a href="https://irishthoracicsociety.com/">https://irishthoracicsociety.com/</a></th>
<th>Criteria</th>
<th>Potential Antiviral Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRS A</strong></td>
<td>SaO2&gt;94%, RR&lt;20 No O2 requirement or nasal cannula &lt;/= 3L</td>
<td>No antiviral</td>
</tr>
<tr>
<td><strong>CRS B, C1, C2</strong></td>
<td>Hospitalised with confirmed COVID-19 AND SaO2&lt;94%, RR&gt;20 B: nasal cannula &gt;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)</td>
<td>Clinical trial* OR 1st Line: Hydroxychloroquine (HCQ) oral: see Table 4. Note: Highly toxic in overdose, especially in children. There is currently insufficient evidence to recommend systematic use of HCQ and azithromycin in combination for the treatment of COVID-19. Any case being considered for combination treatment should be reviewed with local Infectious Diseases or Clinical Microbiology team with consideration of the safety profile of the combination, including the potential for QTc prolongation, in individual patients. See Table 3 for information on azithromycin which includes criteria for ECG monitoring. 2nd Line: If 1st line option 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: <a href="https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/">https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/</a></td>
</tr>
<tr>
<td><strong>CRS D</strong></td>
<td>Hospitalised with confirmed COVID-19 AND SaO2&lt;94%, RR&gt;20 and poor response to HFNO/ NIV ICU +/- intubation</td>
<td>Clinical trial* OR Remdesivir (intravenous): see Table 6. 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: <a href="https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/">https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/</a></td>
</tr>
</tbody>
</table>
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.

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.
This information is valid only on the day of printing, for any updates please check: https://www.hpsc.ie/a-z/respiratory/novelcoronavirus/guidance/guidanceforhealthcareworkers/

**Table 3 Azithromycin for the treatment for confirmed COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.**

|------|--------------------------|--------------------|------------|--------------------------|-------------|------------------------|------------------------|
| Azithromycin | **Insufficient evidence to recommend systematic use of HCQ and azithromycin combination for the treatment of COVID-19. Cases being considered for combination treatment should be reviewed with local Infectious Diseases or Clinical Microbiology team. Consider safety profile of the combination, including the potential for QTc prolongation, in individual patients.** | **In vitro antiviral activity reported against Zika and Ebola viruses.** | **Hypersensitivity: monitor for allergic reactions (including anaphylaxis) & dermatological reactions.** | **Renal Impairment:**  
GFR>10ml/min: Dose as in normal renal function.  
GFR<10ml/min: Dose as in normal renal function. 33% increase in exposure has been reported if GFR<10ml/min; manufacturer advises use with caution. | **See Summary of Product Characteristics (SmPC) for full list of 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/).** | Available formulations:  
- 250mg tablets and capsules  
- 200mg/5mL powder for oral suspension.  
Oral suspension recommended for enteral feeding tubes – no need to stop feed. |

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

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Table 3 (continued from previous page) Azithromycin for the treatment for confirmed COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.

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<tr>
<td>Azithromycin</td>
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<tr>
<td>Dose: 500mg ONCE a day for THREE days (used in combination with HCQ on D1-3). Take 1 hour before or 2 hours after food.</td>
<td></td>
<td>Myasthenia gravis: may aggravate myasthenia gravis.</td>
<td></td>
<td>Hepatic Impairment:</td>
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<td></td>
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<td>Clostridium difficile Associated Diarrhoea (CDAD): possible with all antibacterials, including azithromycin.</td>
<td></td>
<td>Metabolised in the liver and excreted in the bile. Use with caution if significant hepatic disease; no data in severe hepatic impairment.</td>
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<td></td>
<td>Diabetes Mellitus: 5 ml of the reconstituted Zithromax® oral suspension contains 3.87 g of sucrose; caution advised in patients with Diabetes Mellitus.</td>
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Infectious Diseases or treatment should be considered for treatment of COVID-19 combination for the and azithromycin systematic use of HCQ to recommend Insufficient evidence consensus.

Unlicensed indication, included from expert consensus. Insufficient evidence to recommend systematic use of HCQ and azithromycin combination for the treatment of COVID-19. Cases being considered for combination treatment should be reviewed with local Infectious Diseases or Clinical Microbiology team. Consider safety profile of the combination, including the potential for QTc prolongation, in individual patients.

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<tbody>
<tr>
<td>Unlicensed indication, included from expert consensus. Insufficient evidence to recommend systematic use of HCQ and azithromycin combination for the treatment of COVID-19. Cases being considered for combination treatment should be reviewed with local Infectious Diseases or Clinical Microbiology team. Consider safety profile of the combination, including the potential for QTc prolongation, in individual patients.</td>
<td>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.</td>
<td>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 &lt;6 years of age (200mg tablets not adapted for weight &lt;35kg).</td>
<td>Full Blood Count: Myelosuppression may occur rarely; monitor if pre-existing myelosuppression or if receiving other myelosuppressive agents concommitantly. 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). Blood glucose: may cause hypoglycaemia. Epilepsy: may lower seizure threshold.</td>
<td>Renal Impairment: Dose adjustment in renal impairment: CrCl 30-50mL/min: D1: 400mg BD; D2: 200mg BD; D3-5: 200mg OD. CrCl 10-30mL/min or CrCl &lt;10mL/min or Haemodialysis or Haemodiafiltration or CVVHD: D1: 400mg OD; D2-5: 200mg OD Hepatic Impairment: No specific dose adjustments recommended – use with caution.</td>
<td>See Summary of Product Characteristics (SmPC) for full list of side-effects; available from: <a href="https://www.medicines.ie/medicines/plaquenil-tablets-33380/smpc">https://www.medicines.ie/medicines/plaquenil-tablets-33380/smpc</a> 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 (<a href="http://www.covid19-druginteractions.org/">http://www.covid19-druginteractions.org/</a>). Caution with concomitant QTc prolonging agents. Caution advised if considering azithromycin + HCQ combination in patients with risk factors for QTc prolongation or who are receiving medications that might interact to cause arrhythmias. 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</td>
<td>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.</td>
<td></td>
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</table>

**Table 4 Hydroxychloroquine (HCQ) for the treatment for COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.**
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<td><strong>Recommended Dose:</strong></td>
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<tr>
<td>Day 1: 400mg TWICE a day; Days 2-5 200mg TWICE a day (total duration 5 days).</td>
<td></td>
<td>Lapp lactase deficiency or glucose-galactose malabsorption.</td>
<td></td>
<td>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.</td>
<td></td>
<td><strong>LFTs:</strong> abnormal LFTs have been reported (uncommon).</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 (continued from previous page) Hydroxychloroquine (HCQ) for the treatment for COVID-19. See Summary of Product Characteristics (SmPC) for full prescribing information.
### Table 5: Lopinavir/ritonavir for the treatment of COVID-19 (adapted from St James’s Hospital Protocol). See Summary of Product Characteristics (SmPC) for full prescribing information.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>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.</td>
<td>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.</td>
<td>Liver Function Tests (LFTs): deranged liver function tests and hepatic dysfunction have been reported; monitor LFTs before and during treatment.</td>
<td>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.</td>
<td>See Summary of Product Characteristics (SmPC) for full list of side-effects; available from: <a href="https://www.medicines.ie/medicines/kaletal-200-mg-50-mg-film-coated-tablets-32560/smpc">https://www.medicines.ie/medicines/kaletal-200-mg-50-mg-film-coated-tablets-32560/smpc</a>.</td>
<td>Refer to SmPC and drug-drug interaction databases e.g. Stockley’s and University of Liverpool online (<a href="http://www.covid19-druginteractions.org/">http://www.covid19-druginteractions.org/</a>)</td>
<td>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.</td>
</tr>
</tbody>
</table>


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|------|--------------------------|--------------------|------------|--------------------------|-------------|-----------------------|-----------------------|
| Lopinavir/ritonavir | Lopinavir/ritonavir | 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. | 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. |}

Contd. Oral solution is preferable in patients unable to swallow solid dosage forms.

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 milk (not water).

Incompatible with polyurethane feeding tubes: Compatible with: polyvinyl chloride (PVC) and silicone feeding tubes.
Table 6 Remdesivir for the treatment of COVID-19

<table>
<thead>
<tr>
<th>Drug – Remdesivir</th>
<th>Proposed MOA in COVID-19</th>
<th>Key Information</th>
</tr>
</thead>
</table>
|                   | 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. | - Remdesivir is an investigational medicinal product only available on a compassionate use or via expanded access direct from the manufacturer (Gilead)
- 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 EMP 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:
  - Gilead UK Med Info; email: UKMed.Info@gilead.com
  - 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_24Jan.png]

  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.


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References

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 Specialties, including Infectious Diseases / Microbiology / Obstetrics. 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 hyperglycaemia.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

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<td>COVID19</td>
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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.

Azithromycin in Pregnancy

Although limited, available data on the use of azithromycin in pregnancy do not suggest an increased risk of congenital malformation, preterm delivery or low birth weight. The considerable data for macrolides as a class of antimicrobial agents provide further reassurance; available data do not suggest an increased risk of congenital malformations, cardiac malformations, preterm delivery, low birth weight and neonatal complications. An increased risk of spontaneous miscarriage has been reported for certain macrolides but may be explained by confounding by indication as other antibiotics have also been associated with increased risks.

Where azithromycin 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.

Pregnancy References

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).