Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

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

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of hospitalised patients with confirmed COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

This guidance should be read in conjunction with the National HSE Infection Prevention and Control (IPC) Guidance for Possible or Confirmed COVID-19 .

This guidance document is informed by the COVID-19 ERG *Rapid Evidence Review* for "Clinical evidence for the use of antivirals in the treatment of COVID-19 v13" published 22nd Oct 2020 (available from: http://www.ncpe.ie/research/covid-19/) and the WHO *Therapeutics and COVID-19: living guideline* published 20 Nov 2020 *(*available from: https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline).

The following HSE interim guidance and advisory statements should also be considered for the management of patients with COVID-19, as appropriate:

- COVID-19 Interim Clinical Guidance - VTE protocol and patient information for acute hospitals (available from: https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866382)

The following interim guidance and advisory statements available from https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/ :

- HSE Interim Guidance for the use of Systemic Corticosteroids in the Management of Hospitalised Patients with Severe COVID-19 Disease
- *HSE Interim Advisory Statement for the use of Tocilizumab in the Management COVID-19.*
- *HSE Interim Position Statement on the Use of Human Normal Intravenous Immunoglobulin (IVIg) in the Management of COVID-19.*

Key changes to Version 6:

- Recommendations regarding remdesivir updated in response to:
  a. The most recent publication of the WHO *Therapeutics and COVID-19: living guideline.*
  b. European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended change to the terms of the marketing authorisation for remdesivir (Veklury®).
- Details regarding the remdesivir Compassionate Use Programme have been updated.
- The format and structure of the guidance document has been reconfigured.

Refer to **Appendix 1** for guidance on the differential diagnoses and treatment of respiratory tract infection in patients presenting with suspected COVID-19.

At present, prescribing of antivirals for the management of patients with confirmed COVID-19 disease should be **restricted to hospitals only**.

Section 1: Key Recommendations

Remdesivir: The HSE recommends that the use of remdesivir for the management of COVID-19 should be primarily in the setting of an ethically approved clinical trial.

However, it is acknowledged that there is an absence of universal access to clinical trials. If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion in a multidisciplinary setting with patient engagement.

Patients (or their relevant person, by phone) should be adequately informed about the uncertain efficacy and potential toxicities, and given an opportunity to indicate their values and preferences.

See **Section 2** for further information.

Lopinavir/ritonavir: Not recommended as a therapeutic agent outside of clinical trials due to evidence indicating a lack of benefit in patients hospitalised with COVID-19.

Hydroxychloroquine: Not recommended as a therapeutic agent outside of clinical trials due to evidence indicating a lack of benefit in patients hospitalised with COVID-19.

Azithromycin: Not recommended in combination with hydroxychloroquine in the context of COVID-19 due to its lack of proven clinical efficacy and safety concerns in COVID-19.

Section 2 Remdesivir Prescribing Information

Clinical Trials

The HSE recommends that the use of remdesivir for the management of COVID-19 should be primarily in the setting of an ethically approved clinical trial. Information on on-going clinical trials, including those recruiting, is available on the EU CT Register for COVID trials (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19) or www.clinicaltrials.gov.

Treatment outside of a clinical trial

If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion in a multi-disciplinary setting with patient engagement.

Remdesivir has received a conditional marketing authorisation from the European Commission. This means that the benefits and risks of treatment are under active review, and the product information is updated on a regular basis, to take account of new efficacy and safety information.

Patients (or their relevant person, by phone) should be adequately informed about the uncertain efficacy and potential toxicities, and given the opportunity to indicate their values and preferences.

For full prescribing information refer to the Summary of Prescribing Characteristics (SmPC), available at: https://www.ema.europa.eu/en/medicines/human/EPAR/veklury .

Table 1 Treatment Criteria for Patients Treated Outside of a Clinical Trial.

For full prescribing information refer to the Summary of Prescribing Characteristics (SmPC).

Considering the best available evidence the following criteria, in addition to the prescribing recommendations detailed in the SmPC, should be satisfied if treatment outside of a clinical trial is being considered:

- Hospitalised with coronavirus disease 2019 (COVID-19)
- Patients with pneumonia requiring supplemental oxygen at the start of treatment (low- or high-flow oxygen or other non-invasive ventilation). Remdesivir is not indicated for patients requiring invasive forms of ventilatory support at the start of treatment.
- Multi-disciplinary team assessment should determine if patients not suitable for escalation would benefit from initiation of treatment with remdesivir.
- If patients on remdesivir require escalation, continuation of the drug should be considered by multi-disciplinary team assessment.

Table 2 Duration of Treatment for Patients Treated Outside of a Clinical Trial.

The HSE recommends a total duration of 5 days of remdesivir. Available evidence has shown no incremental benefit of 10 days treatment over 5 days. See COVID-19 ERG *Rapid Evidence Review* for "Clinical evidence for the use of antivirals in the treatment of COVID-19 v13" for further information (available from: http://www.ncpe.ie/research/covid-19/).

Table 3 Access to Remdesivir Supply

1. Clinical Trials: The WHO Solidarity trial is currently open to recruitment across multiple acute hospitals in Ireland. The trial is an international collaboration amongst WHO and participating international member countries and researchers to evaluate potential COVID-19 treatments. Remdesivir is included as an arm in this study.

2. On 15th December 2020, the HPRA confirmed that the Compassionate Use Programme for remdesivir has now closed. Requests for further information should be directed to the manufacturer, contact details are:
    - Gilead UK Med Info; email: UKMed.Info@gilead.com
    - UKICOVID-19; email: UKICOVID-19@gilead.com

3. Consult with the hospital Pharmacy Department for other supply access.

Appendix 1 Differential Diagnoses and Treatment of Respiratory Infections in Presentation of Suspected Cases of COVID-19.

Adapted from St James's Hospital Protocol) – considering the principles of antimicrobial stewardship https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/antimicrobialstewardship/		
	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.	If confirmed COVID-19 refer to this guidance and other HSE COVID-19 related guidance detailed on page 4.

Appendix 2: 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. The priority for medical care should be to stabilise the woman's condition with standard therapies.[4] As highlighted in multiple maternal death enquiries from Ireland and the UK, pregnant or postpartum women with medical problems should not be denied investigations and treatment because they are pregnant or breastfeeding and should be treated the same as non-pregnant women unless there is a clear contra-indication.[5]

The management of pregnant women with acute respiratory infection with COVID-19 should be in line with national guidance for non-pregnant patients, as detailed in the main body of this document. The use of pharmacological agents in the treatment of COVID-19 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 or unknown risks to the mother or the foetus from the drug. If treatment is indicated, pregnant and postpartum women should not be excluded from clinical trials unless there is a clear contra-indication.[5]

The use of pharmacological agents outside of a clinical trial should balance the limited evidence of the safety of these agents in pregnancy with the uncertain efficacy. If treatment is being considered outside of a clinical trial, it must only be initiated after consultant-level discussion with multidisciplinary input with from relevant specialities, including Infectious Diseases / Microbiology / Obstetrics / Respiratory and patient engagement.

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

Remdesivir in pregnancy

Extremely limited information is available on the use of remdesivir in human or animal pregnancy. Nonclinical reproductive toxicity studies demonstrated no adverse effect on embryofetal development when remdesivir was administered to pregnant rats and rabbits at exposure that was 4 times the recommended human dose (RHD).[6] A randomised controlled trial of remdesivir use in the treatment of EBOLA included 6 women who had a positive pregnancy test (timing of exposure is unreported). No information on adverse pregnancy outcomes is described.[7]

A number of case reports[8-10] and two case series including 17[11] and 67[12] women, have described the use of remdesivir in pregnant women[11,12]. No particular concerns have been reported in relation to the safety of remdesivir in pregnancy; however the absence of data on the use of remdesivir in the first trimester limits these conclusions.

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
3. European Centre for Disease Prevention and Control (ECDC). Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – sixth update – 12 March 2020. Stockholm: ECDC; 2020.
4. Royal College of Obstetricians and Gynaecologists. The Royal College of Midwives. Coronavirus (COVID-19) Infection in Pregnancy. Information for healthcare professionals. Version 12. Oct 2020.
5. Knight M, Bunch K, Cairns A, Cantwell R, Cox P, Kenyon S, Kotnis R, Lucas DN, Lucas S, Marshall L, Nelson-Piercy C, Page L, Rodger A, Shakespeare J, Tuffnell D, Kurinczuk JJ on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care Rapid Report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK March – May 2020 Oxford: National Perinatal Epidemiology Unit, University of Oxford 2020.
6. Food and Drug Administration (FDA). Fact sheet for health care providers Emergency Use Authorisation (EUA) for Remdesivir (GS-5734™). Accessed online at: fda.gov. Date accessed 20 May 2020.
7. Mulangu S, Dodd LE, Davey RTJ, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019 Dec; 381(24):2293–303.
8. Maldarelli GA, Savage M, Mazur S, Oxford-Horrey C, Salvatore M, Marks KM. Remdesivir treatment for severe COVID-19 in third-trimester pregnancy: Case report and management discussion. Open forum infectious diseases 2020 Sep;7(9).
9. Naqvi M, Zakowski P, Glucksman L, Smithson S, Burwick RM. Tocilizumab and Remdesivir in a pregnant patient with coronavirus disease 2019 (COVID-19). Obstetrics & Gynecology. 2020 Nov 1;136(5):1025-9.
10. Anderson J, Schauer J, Bryant S, Graves CR. The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. Case Reports in Women's Health. 2020 May 16:e00221.
11. Pierce-Williams RA, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, Penfield CA, Roman AS, DeBolt CA, Stone JL, Bianco A. Clinical course of severe and critical COVID-19 in hospitalized pregnancies: a US cohort study. American Journal of Obstetrics & Gynecology Mfm. 2020 May 8:100134.
12. Burwick RM, Yawetz S, Stephenson KE, Collier AR, Sen P, Blackburn BG, Kojic EM, Hirshberg A, Suarez JF, Sobieszczyk ME, Marks KM. Compassionate use of remdesivir in pregnant women with severe COVID-19. Clinical Infectious Diseases. 2020 Oct 8.

Appendix 3: A Proposed Core Outcome Measure Set for Clinical Studies of COVID-19 Infection.

Graphic contains recommendations from the WHO Clinical Characterization and Management Working Group, http://www.comet-initiative.org/Studies/Details/1528 . Refer to HSE COVID 19 Dataset specification for additional information on clinical coding detail.
https://www.hse.ie/eng/services/news/newsfeatures/covid19-updates/covid-19-dataset-specification-for-patient-assessment-and-tracking.pdf

Viral burden
Semiquantitative viral RNA of severe acute respiratory syndrome coronavirus 2 as measured by quantitative PCR or cycle threshold; nasopharyngeal swabs are associated with the highest viral load

Survival
All-cause mortality at hospital discharge or at 60 days

Clinical progression
WHO Clinical Progression Scale measured daily over the course of the study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and 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
Dead	Dead	10

Appendix 4: Guideline Review Group

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