COVID-19 Therapies: What Pharmacist Need to Know

Kathleen Jodoin, Pharm.D., BCPS
Clinical Coordinator, ASP Pharmacy Lead
Mount Sinai Medical Center

1

Disclosures

Dr. Jodoin is a part of the COVID-19 Speaker's Bureau for Gilead Sciences

2

Objectives

1. Describe the pathophysiology of COVID-19
2. Review current guidelines and recommendations for COVID-19 management
3. Assess the role of pharmacists in COVID-19 prevention and management
4. Provide an overview of recent clinical studies, including emerging therapies for COVID-19 management

3

Introduction

- At the end of 2019, a novel coronavirus (SARS-CoV2) was identified as the cause of a cluster of pneumonia cases in Wuhan, China
- February 2020, WHO named the disease COVID-19
- March 2020, WHO declared COVID-19 a global pandemic
- The NIH COVID-19 Treatment Guidelines were Developed in response to the COVID-19 Public Health Emergency declared by the US Department of Health and Human Services in late January 2020. The first version was issued on April 21, 2020 with a final update Feb 29, 2024
- The Federal COVID-19 Public Health Emergency ended in May 2023 and several professional society currently provide COVID-19 treatment guidelines for their medical specialties or subspecialities

National Institutes of Health. Update February 29, 2024. Accessed March 26, 2025. https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

4

COVID-19 Is a Significant Health Issue

UNITED STATES

> 103 million cases

> 1.2 million deaths

GLOBAL

>777 million cases

> 7 million deaths

Includes data from Q1 2020 – March 2025

Number of hospitalizations due to SARS-CoV-2 in last 28 days

United States of America, 28 days to 9 March 2025

Country	Reported COVID-19 related hospitalizations
World	8.6k
United States of America	3.1k

Word Health Organization. Updated March 8, 2025. Accessed March 26. 2025. https://data.who.int/dashboards/covid19/hospitalizations?m49=840&n=o

5

COVID-19 Virus Ongoing Evolution and Vaccination Trends

The virus is **constantly evolving through mutations**, potentially increasing or decreasing[1]:

1. Infectiousness
2. Virulence
3. Ability to evade immunity conferred by vaccines or infections

Low vaccination trends leave some populations at risk

Uptake of the 2023-2024 COVID-19 vaccine in the US[2]

- ~ 7% of **children** age 6 months to 17 years
- ~14.8-16.4% of adults aged **18 to 49 years**
- ~35.6-39.2% of adults aged **≥ 65 years**

1. National Institutes of Health. Updated February 29, 2024. Accessed September 27, 2024. https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf **2.** Centers for Disease Control and Prevention. Updated Nov 15, 2024. Accessed March 26, 2025 https://www.cdc.gov/covidvaxview/interactive/adults.html

6

COVID-19 An Ongoing Public Health Concern

- Despite gradual declines in COVID-19 incidence and mortality, the WHO acknowledged that COVID-19 is a continued threat to health lives and health systems in 2024[1]
- COVID-19 remains a significant cause of mortality in the United States[2]
- COVID-19 related deaths **disproportionately affects individuals** who are Hispanic, Non-Hispanic Black, Non-Hispanic American Indian/Alaskan Native[3]
- Patients with **2 to 5 underlying conditions** have an **estimated 2.55 x higher risk for death** (95% CI, 2.32 to 2.80) compared to those with no reported underlying medical conditions[4]
- People age > 65 years account for 63% of related hospitalizations related to COVID-19 and 88% of in-hospital deaths related to COVID-19[5]

WHO = World Health Organization 1. WHO. 2024. Available at: https://www.who.int/publications/m/item/covid-19-who-health-emergency-appeal-2024. Accessed 26 March 2025. 2. Centers for Disease Control and Prevention. Deaths by week and state: provisional death counts for COVID-19. Accessed March 26, 2025. www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm; 3. Lopez L 3rd, Hart LH 3rd, Katz MH. Racial and ethnic health disparities related to COVID-19. *JAMA*. 2021;325(8):719-720; 4. Kompaniyets L, Pennington AF, Goodman AB, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020-March 2021. *Prev Chronic Dis.* 2021;18:E66. 5. Taylor CA, Patel K, Patton ME, et al; COVID-NET Surveillance Team. COVID-19–associated hospitalizations among U.S. adults aged ≥65 years. *MMWR Morb Mortal Wkly Rep*. 2023;72(40):1089-1094.

7

Comorbidities associated with high risk for severe COVID-19

Cancer	Liver disease
Chronic kidney disease	Overweight and obesity
Chronic lung diseases	Pregnancy
Dementia or other neurological conditions	Sickle cell disease or thalassemia
Diabetes (type 1 or type 2)	Smoking, current or former
Down syndrome	Solid organ or blood stem cell transplant
Heart conditions	Stroke or cerebrovascular disease
HIV infection	Substance use disorders
Immunocompromised state	

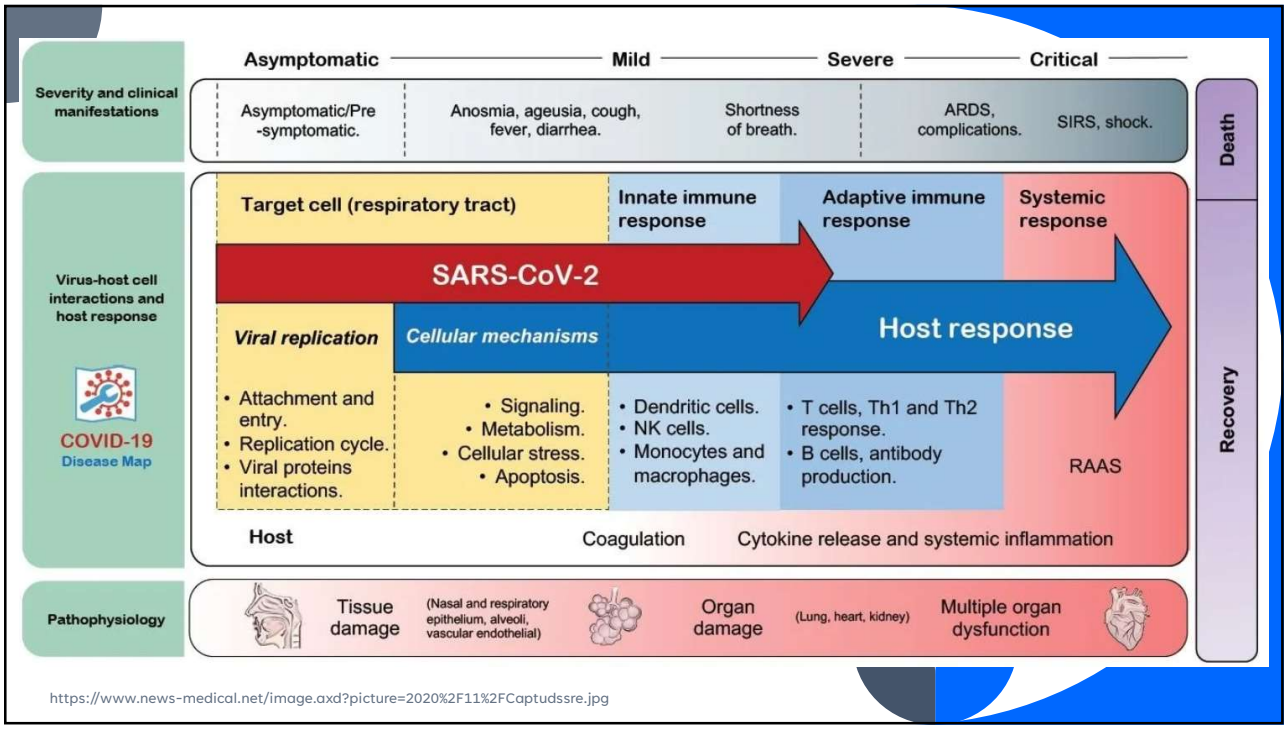
MDedge News

Note: "Severe" defined as hospitalization, admission to intensive care unit, intubation or mechanical ventilation, or death.

Source: Centers for Disease Control and Prevention

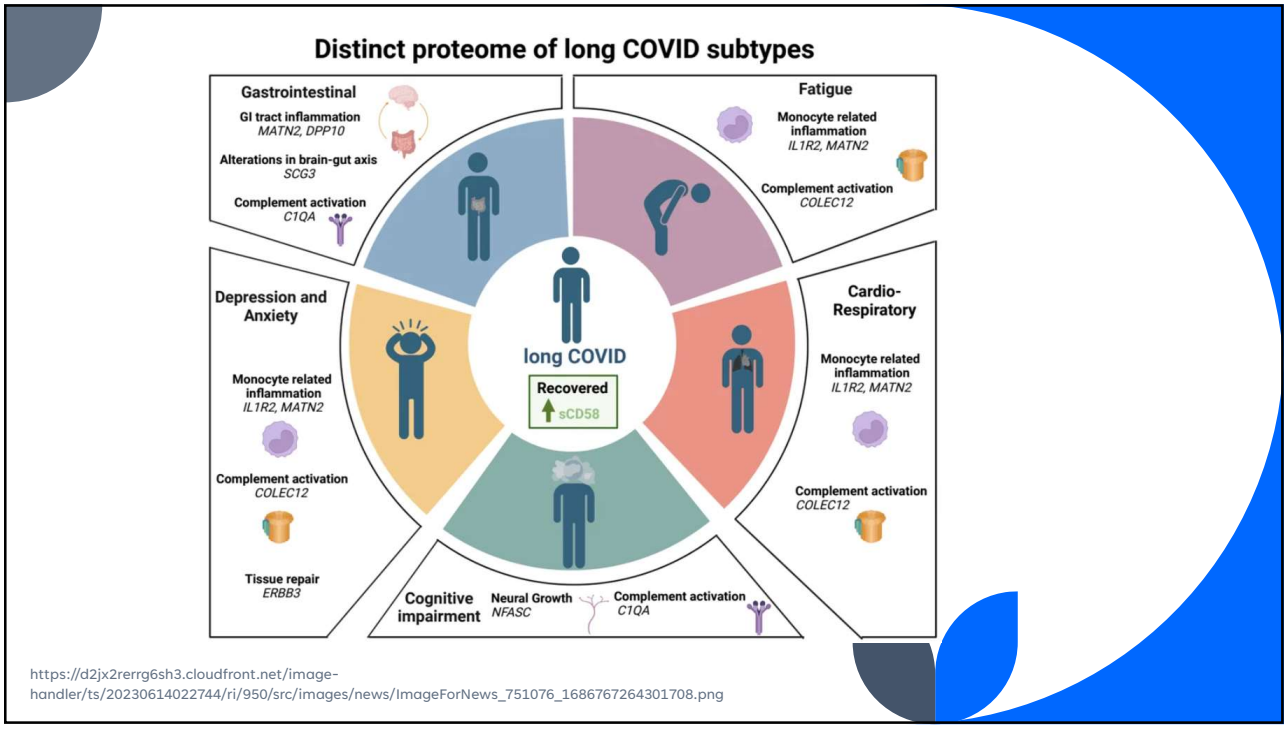
For a full list of risk factors, see https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

8



https://www.news-medical.net/image.axd?picture=2020%2F11%2FCaptudssre.jpg

9



https://d2jx2rerrg6sh3.cloudfront.net/image-handler/ts/20230614022744/ri/950/src/images/news/ImageForNews_751076_1686767264301708.png

10

Inpatient Treatment Trends

Emerging real-world evidence shows that **prescribing practices may not be consistent with recommendations from treatment guidelines**

Study presented at ECCMID April 2024 reviewed 151,214 patients hospitalized for COVID-19

About half of the patients not requiring supplemental oxygen at baseline, received DEX in the first 2 days of hospitalization despite recommendation from guidelines against the use of DEX for these patients

Of the 36,489 patients that received DEX monotherapy at hospital admission:

RDV was not initiated in 37% (n=12,206) of the patients on LFO or 16% (n=5,328) of patients on HFO/NIV during subsequent days in the hospital despite current guideline recommendations to use RDV in these patients

ECCMID = European Society of Clinical Microbiology and Infectious Diseases; RDV = remdesivir; DEX = dexamethasone; LFO = low flow oxygen; HFO/NIV = high flow oxygen/non-invasive ventilation

ECCMID2024_Mozaffari_AQO0704_RDV-Dexamethasone_V3_FINAL.pdf

11

NIH Guideline Recommendations for Adults with COVID-19 Who Do Not Require Supplemental Oxygen

Non-hospitalized or Hospitalized for Reasons Other Than COVID-19

Preferred therapies in order of preferences:

Ritonavir-boosted nirmatrelvir (AIIa)[a-c]

Remdesivir (BIIa)[a,b,d]

Alternative therapy:

Molnupiravir (CIIa)[b,e,f]

Against use of dexamethasone or other systemic corticosteroids (AIIb)[g] unless these agents are being used to treat an underlying condition (AIII)

Hospitalized for COVID-19

Remdesivir[h] for patients who are:

- Immunocompromised (BIIb)
- At high risk for other reasons (BIII)

Against use of dexamethasone (AII) **or other systemic corticosteroids** (AIII)[i]

12

NIH Guideline Recommendations for Adults with COVID-19 Who Require Supplemental Oxygen

Conventional Oxygen

Remdesivir + dexamethasone (BIIa)[a,b].

Patient receiving dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add

- **PO baricitinib** (BIIa) **or IV tocilizumab** (BIIa)

Alternative: **IV abatacept** (CIIa) or **IV infliximab** (CIIa)

HFNC OXYGEN or NIV

Dexamethasone (AI). If not already initiated promptly add 1 of the following immunomodulators:

- Preferred: **PO baricitinib** (AI)
- Preferred alternative: **IV tocilizumab** (BIIa)
- *Alternatives*: IV abatacept or IV infliximab (CIIa)

Add **remdesivir** in certain patients, including:

- Immunocompromised (BIIb)
- Evidence of ongoing viral replication (BIII)
- ≤ 10 days of symptoms (CIIa)

MV or ECMO

Dexamethasone (AI). If patient has not already received a second immunomodulator, promptly add:

- **PO baricitinib** (BIIa) or
- **IV tocilizumab** (BIIa)

Insufficient evidence for or against **remdesivir**

13

COVID-19 Antivirals

14

Ritonavir-boosted nirmatrelvir (Paxlovid™): Overview

- Nirmatrelvir: inhibits SARS-CoV-2 main protease to block viral replication
- Ritonavir: inhibits CYP3A-mediated metabolism of nirmatrelvir, resulting in increased nirmatrelvir plasma concentrations.
- Approved for treatment of **mild to moderate COVID in adults** who are at high risk for progression to severe disease
- **Initiate within 5 days of symptom onset**
- Dosing
  - **Standard**: 300mg/100mg oral BID x 5 days
  - **Renal Adjustment**: eGFR 30-59 reduce to 150/100mg; avoid if eGFR < 30 ml/min per manufacturer - retrospective data in limited number of patients available[1]

1. Chan GCK, Lui GCY, Wong CNS, et al. Safety profile and clinical and virological outcomes of nirmatrelvir-ritonavir treatment in patients with advanced chronic kidney disease and coronavirus disease 2019 (COVID-19). *Clin Infect Dis*. Published online August 2, 2023. doi:10.1093/cid/ciad371

15

Ritonavir-boosted nirmatrelvir (Paxlovid™): Key Considerations

- **Major CYP3A4 interactions** (due to ritonavir)
  - **Common medications affected:** statins, antiarrhythmics, immunosuppressants, anticoagulants
  - Requires careful medication reconciliation and management. Some potential drug interactions may be mitigated by **holding or dose reducing the comedication**
- **Storage and Dispensing**
  - Dispensing packs – each pack contains 10 single dose blister cards, full 5-day course
  - One renal dose, one regular (do not mix up)
  - Logistical considerations if providing for inpatient use
- **Adverse Effects**: Dysgeusia (altered taste), diarrhea, elevated liver enzymes, possible rebound COVID symptoms

16

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers

Other Drugs with Established and Other Potentially Significant Drug Interactions with PAXLOVID (listed alphabetically by generic name)

Interaction Codes:

XXX	Coadministration of this drug with PAXLOVID is CONTRAINDICATED. For further information, refer to the Fact Sheet for Healthcare Providers and the individual Prescribing Information for the drug.
***	Coadministration of this drug with PAXLOVID should be avoided and/or holding of this drug, dose adjustment of this drug, or special monitoring is necessary. Consultation with the prescriber of the potentially interacting drug is recommended. For further information, refer to the Health Care Provider Fact Sheet, the USPI, and the individual Prescribing Information for the drug.

PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers, 9/12/2024. https://access.msmc.com/Citrix/MSMCWeb/clients/HTML5Client/src/SessionWindow.html?launchid=1743241469068

17

Ritonavir-boosted nirmatrelvir (Paxlovid™): Key Considerations

Rebound

- Some patients experience a **recurrence of symptoms and/or test positively** 2-8 days **after completing treatment**
- Usually mild and self-limiting, not associated with severe outcomes
- Theories: Insufficient duration for some patients, blunted immune response due to early viral suppression, host factors rather than drug resistance or viral mutation
- CDC guidance – **no additional antiviral treatment needed for rebound unless clinically indicated**
  - Symptoms mild and improving, afebrile, positive test without symptoms vs. clinical deterioration, immunocompromised, prolonged rebound course

18

Ritonavir-boosted nirmatrelvir (PaxlovidTM): Pivotal Trial Summary

- Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients **(EPIC-HR):** randomized, double-blind, placebo-controlled study in unvaccinated, non-hospitalized adult patients with COVID-19 and at least one risk factor for progression to severe diseases. Symptoms were less than or equal to 5 days.
- **COVID-19 related hospitalization or death** by Day 28 **was lower** in the treatment (n=1,361) vs. placebo group (n=1,120) **by 5.81%** (95% CI -7.78 to -3.84: P<0.001; **relative risk reduction 88.9%**)

Hammond J., Leister-Tebbe H., Gardner A. et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19. Feb 16, 2022. N Engl J Med 2022; 386: 1397-1498. https://www.nejm.org/doi/full/10.1056/NEJMoa2118542

19

Molnupiravir (Lagevrio™)

- Molnupiravir metabolized to cytidine analog, incorporating in SARS-CoV-2 viral RNA and inhibiting replication.
- For **mild to moderate COVID-19** in non hospitalized adults who are at high risk for progression to severe disease
- **Use within 5 days of symptom onset**
- Dose: 800mg PO every 12 hours x 5 days
- **No** renal or hepatic **dose adjustments** needed, **no known** significant CYP mediated **drug interactions**
- Animal studies show fetal harm – **discuss contraceptive precautions as appropriate**

20

Molnupiravir (Lagevrio™) Pivotal Trial Summary

- Molnupiravir for Orla Treatment of COVID-19 in Nonhospitalized Patients **(MOVe-OUT**) randomized, placebo-controlled, double-blind trial
- Molnupiravir (n=716) vs. placebo (n=717) resulted in 30% relative risk **reduction in hospitalization/death vs. placebo**, absolute risk reduction 3% (6.8% vs. 9.7%; 95% CI -5.9 to -0.1)
- **Not as effective as nirmatrelvir-ritonavir**

Bernal A., Gomes de Silva, M., Musungaie D., et al. Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalized Patients. Dec 16, 2021 N Engl J Med 2022; 386:509-520

21

Remdesivir (Veklury®): Overview

- Pharmacologically active form is an adenosine analog that competes for incorporation into viral RNA, disrupting SARS-CoV-2 replication
- Indicated for **adults and pediatric patients** (birth to < 18 years of age weighing at least 1.5kg); **hospitalized and non-hospitalized** patients with mild to moderate COVID 19 who are at high risk for progression to severe COVID-19
- Dose (Adult): 200mg IV x 1 Day 1 followed by 100mg IV Day 2-5 (inpatient) and Day 2-3 (outpatient) – **duration differs based on phase of care**
- Medication label updated to remove renal monitoring, **no renal dose adjustments required** (REDPINE)

Sise M., Santos J., Goldman J. et al. Efficacy and Safety of Remdesivir in People with Impaired Kidney Function Hospitalized for COVID-19 Pneumonia: A Randomized Clinical Trial. Clin Infect Dis. 2024 Nov 22; 79 (5): 1172-1181.

22

PINETREE

- Randomized, double-blind, placebo-controlled clinical trial
- 562 patients who were **not hospitalized** and were at high risk for disease progression with confirmed SARS-CoV-2 infection and showed symptoms of **mild-to-moderate COVID-19 for ≤ 7 days**[1]

NIAID ACTT-1

- Randomized, double-blind, placebo-controlled clinical trial
- 1,062 adult patients **hospitalized** with confirmed SARS-CoV2 infection and **mild, moderate, or severe COVID-19**[2]

NIAID = National Institute of Allergy and Infectious Disease

1. Gottlieb RL, et al. *N Engl J Med*. 2022;386(4):305-315
2. Beigel JH, et al. *N Engl J Med*. 2020;383(19):1813-1826.

23

Pivotal Trials Summary

PINTREE

- Patients received remdesivir (n=279) or placebo (n=283) for 3 days. The primary endpoint was composite of COVID-19 related hospitalization or death from any cause by Day 28
- **87% lower risk for COVID-19 related hospitalization or death from any cause in patients who received remdesivir** (0.7% in remdesivir group COVID-19 vs. 5.3% in placebo group [HR 0.13; 95% CI, 0.02 to 0.59])
- **No deaths occurred in either arm**. Risk reduction was driven solely by reduction in risk of hospitalization
- Adverse reaction frequency was comparable between remdesivir and placebo

1. Gottlieb RL, et al. N Engl J Med. 2022;386(4):305-315

24

Pivotal Trial Summary

NIAID ACTT-1

- Laboratory abnormalities and adverse reaction frequency was comparable between remdesivir and placebo
- Patients received remdesivir (n=541) or placebo (n=521) for up to 10 days. The primary endpoint was time to recovery within 29 days after randomization
  - **Patients experienced 5 days shorter time to recovery with remdesivir.** Median time to recovery was 10 days with remdesivir vs. 15 days with placebo (recovery rate ratio 1.29 [95% CI, 1.12 to 1.49] p < 0.001)
- Secondary endpoints
  - **Remdesivir reduced progression to new oxygen support**
    - Incidence of new use of NIV or high-flow oxygen was 29% lower in the remdesivir vs. placebo (17% [95% CI, 13 to 22] vs. 24% [95 CI, 19 to 30])
    - Incidence of new MV or ECMO use was 43% lower in the remdesivir vs. placebo (13% [95% CI, 10 to 17] vs. 23% [95% CI, 19 to 27])

Beigel JH, et al. N Engl J Med. 2020;383(19):1813-1826.

25

Pivotal Trial Summary

NIAD ACTT-1: Secondary Endpoints (continued)

- Overall mortality results were not statistically significant (mortality at Day 29 11% remdesivir vs. 15.2% placebo HR 0.73 [95% CI 0.52 to 1.03])
- Post hoc subgroup analysis showed remdesivir was associated with a mortality reduction in patients on low-flow oxygen at baseline (ordinal score 5, HR: 0.30 [95% CI 0.14 to 0.64])
- Table S11 (provides data on recovery and mortality)

26

Pivotal Trial Summary

WHO SOLIDARITY

- Open-label, multicenter, randomized clinical trial conducted in 35 countries in adult patients (n=8,275) who were hospitalized with COVID-19
- Primary outcome was in-hospital mortality, overall and subdivided by disease severity (defined by supplemental oxygen use recorded at entry)
- **Mortality in the overall population was not statistically significant** (14.5% remdesivir vs. 15.6% control, rate ratio: 0.91 [95% CI, 0.82 to 1.02], p = 0.12)
- There was a **13% relative risk reduction in mortality observed in patients on supplemental oxygen (low and high flow) in the remdesivir vs. control group** (14.6% vs. 16.3% rate ratio 0.87 [95% CI, 0.76 to 0.99] p = 0.03)

27

Which of the following antiviral therapies are approved for outpatient initiation in patients with COVID-19?

A. Nirmatrelvir-ritonavir (Paxlovid™)

B. Molnupravir (Lagervrio™)

C. Remdesivir (Veklury®)

D. Nirmatrelvir-ritonavir (PaxlovidTM), Molnupiravir (LagervrioTM), and Remdesivir (Veklury®)

E. Nirmatrelvir-ritonavir (Paxlovid™) and Molnupiravir (Lagervrio™) only

28

Which medication is associated with a metallic taste and requires careful review for potential drug-drug interactions?

A. Remdesivir (Veklury ®)
B. Nirmatrelvir-ritonavir (PaxlovidT^{M})
C. Molnupiravir (LagevrioTM)
D. Dexamethasone

29

COVID-19 Immunomodulators

30

Dexamethasone

- In COVID-19, **inflammation in the lungs is a major factor contributing to severe disease**, particularly in patients with severe hypoxia and ARDS.
- The strong anti-inflammatory effects of steroids make them ideal candidates for modulating excessive inflammation in these critically ill patients and reducing or preventing cytokine storm.
- **COVID-19 Dose**: 6mg IV/PO x 10 days (or until discharge if sooner)
- Why Dexamethasone vs. other Steroids?
  - Experience and Familiarity
  - Potency, Long Half-Life, IV and PO options
  - Cost and Accessibility
  - Specific Data from RECOVERY Trial

ARDS = acute respiratory distress syndrome

31

Steroid Conversion

Corticosteroid	Equivalent Dose (mg)	Half-life (hours)
Short-Acting		
Cortisone	25	8-12
Hydrocortisone	20	8-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 - 0.75	36-54
Dexamethasone	0.75	36-54

32

Pivotal Trial Summary

The RECOVERY trial is a large, multicenter, randomized controlled trial conducted in the UK, designed to assess the efficacy of various treatments for COVID-19. It enrolled over **6,000 hospitalized patients** and evaluated several interventions, including **dexamethasone**, **hydroxychloroquine**, **azithromycin**, **tocilizumab**, and more. The primary outcome was **all-cause mortality at 28 days**.

Dexamethasone Results (n=2,104) was the most significant intervention in the trial.

- **Mortality** difference **varied according to the level of respiratory support patients** were receiving at time of randomization.
- The **incidence of death was lower than** that in the usual care group
  - **Among patients receiving invasive mechanical ventilation** (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81)
  - **Among those receiving oxygen** without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94)
- **No benefit** was observed in patients who were **not receiving oxygen,** including those with mild disease or who were not hospitalized (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55).

RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530

33

Dexamethasone

Dexamethasone is a corticosteroid that has been shown to reduce mortality in patients with COVID-19 who require supplemental oxygen or mechanical ventilation. However, it is **not recommended for use** in patients who **do not require supplemental oxygen** because of the following reasons:

- Impact on Clinical Outcomes
  - RECOVERY
- Potential Harmful Effects in Non-Hypoxic Patients
  - Immunosuppression
  - Delayed Recovery
- Risk of Side Effects
  - Fluid retention, hyperglycemia, and elevated blood pressure

34

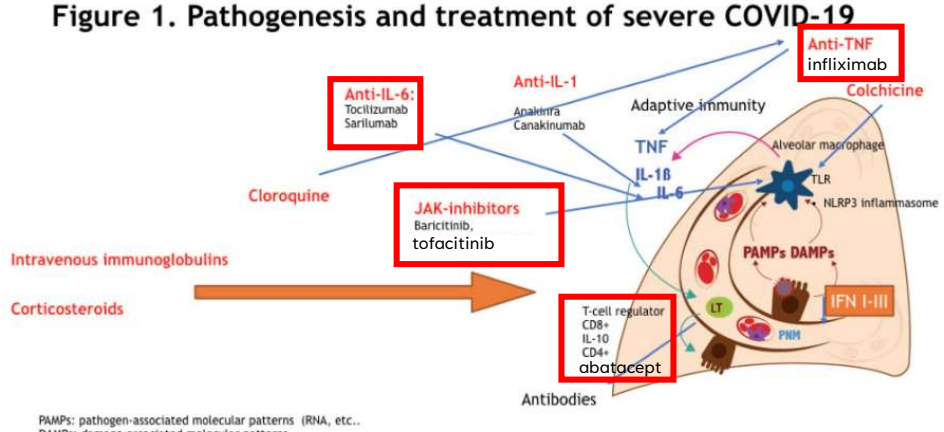
Rheumatology Drugs for COVID-19

- While waiting for the development of specific antiviral therapies and vaccines to effectively neutralize the SARS-CoV2, a relevant therapeutic strategy was to **counteract the hyperinflammatory status**, characterized by an increase of interleukins [mainly (IL)-1β, IL-2, IL-6, IL-7, IL-8] and tumor necrosis factor (TNF)-α, which hallmarks the most severe clinical cases.
- This uncontrolled pulmonary inflammation was suspected to be the main causes of mortality in the severe forms of SARS-CoV-2 infection
- **'Repurposing' immunomodulatory drugs** and applying clinical management approved for rheumatic diseases

Atzeni Fabiloa, Masala Ignazio, Rodriguez-Carrio Javier, et al. The Rheumatology Drugs for COVID-19 Management: Which and When?. Journal of Clinical Medicine. February 16, 2021 Accessed: https://www.mdpi.com/2077-0383/10/4/783

35

Figure 1. Pathogenesis and treatment of severe COVID-19



Atzeni Fabiloa, Masala Ignazio, Rodriguez-Carrio Javier, et al. The Rheumatology Drugs for COVID-19 Management: Which and When?. Journal of Clinical Medicine. February 16, 2021 Accessed: https://www.mdpi.com/2077-0383/10/4/783

36

Baricitinib (Olumiant®)

- **Mechanism of Action (MOA):** Baricitinib is an **Janus kinase (JAK) inhibitor** that works by blocking the activity of JAK1 and JAK2 enzymes. These enzymes are involved in the signaling pathways for inflammatory cytokines such as IL-6, which play a significant role in the immune response in COVID-19.
- **COVID-19 Dose**: 4mg PO once daily x 14 days or hospital discharge, whichever is first
  - Do not initiate if absolute lymphocyte count is < 200 cells/mm^3 or in ANC is < 500 cell/mm^3.

Atzeni Fabiloa, Masala Ignazio, Rodriguez-Carrio Javier, et al. The Rheumatology Drugs for COVID-19 Management: Which and When?. Journal of Clinical Medicine. February 16, 2021 Accessed: https://www.mdpi.com/2077-0383/10/4/783

37

Baricitinib (Olumiant®) Pivotal Trial Summary

ACTT-2 (Adaptive COVID-19 Treatment Trial 2): double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir (n=515) vs. remdesivir alone (n=518) in hospitalized adults with COVID-19.

- Patients receiving baricitinib had a **median time to recovery** of 7 days vs. 8 days with control and a **30% higher odds of improvement in clinical status** at day 15 (odds ratio, 1.3; 95% CI 1.0 to 1.6).
  - Patient receiving HFNC or NIV at enrollment had time to recovery of 10 vs. 18 days (rate ratio for recover 1.51; 95% CI 1.10 to 2.08).
- The 28-day **mortality was not statistically significant:** 5.1% in the treatment group vs. 7.8% in the control group (hazard ratio for death, 0.65; 95% CI 0.39 to 1.09).

1. Kalil A., Patterson T., Mehta A. et al. Baricitinib plus Remdesivir for Hospitalized Adults with COVID-19. https://www.nejm.org/doi/full/10.1056/NEJMoa2031994; 2. Marconi V., Ramanan A., Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19. Lancet Repir Med. 2021 Dec 9(12): 1407-1418 https://pubmed.ncbi.nlm.nih.gov/34480861/

38

Baricitinib (Olumiant®) Pivotal Trial Summary

COV-BARRIER: double-blind, randomized, placebo-controlled trial evaluating baricitinib vs. standard of care (including dexamethasone and remdesivir).

- **No significant reduction in frequency of disease progression (primary endpoint)**, but treatment in addition to standard of care (including dexamethasone) was **associated with reduced mortality in hospitalized adults** with COVID-19 (28-day all cause mortality 8% vs. 13%, 38.2% relative reeducation 95% CI 0.41-0.78; p = 0.0018)

39

Tocilizumab (Actemra®) Overview

- Tocilizumab is a **monoclonal antibody** that targets the **interleukin-6 receptor (IL-6R)**, blocking the action of IL-6, a cytokine that plays a critical role in the inflammatory response during severe COVID-19 infections.
- **COVID-19 Dose**: 8mg/kg (max 800mg) IV x 1. Can give one additional dose if worsening or lack of clinical improvement. Must space administration of doses by at least 8 hours.
  - Do not use if ANC < 1000/mm3, platelets < 50,000/mm3, or ALT/AST > 10 x ULN

40

Tocilizumab (Actemra®) Pivotal Trial Summary

RECOVERY: randomized, controlled, open-label assessing treatment (n=621) vs. standard of care (n=729) in hospitalized COVID-19 patients with hypoxia and evidence of inflammation.

- **Mortality at day 28 was lower** 31% vs. 35% (rate ratio 0.85; 95% CI 0.76-0.94 p=0.0028). Consistent across all prespecified subgroups including those receiving systemic corticosteroids.
- Those receiving tocilizumab were **more likely to be discharged from the hospital** within 28 days (57% vs. 50% rate ration 1.22; 1.12-1.33, p<0.0001)
- Among those not receiving MV at baseline, those allocated tocilizumab were **less likely to reach composite endpoint of MV or death** (35% vs 42%; risk ratio 0.82; 95% CI 0.77-0.92; p<0.0001)

41

Tocilizumab (Actemra®)

REMAP-CAP: ongoing international, multifactorial, adaptive platform trial. Evaluated sarilumab (n=48) vs. tocilizumab (n=353) vs. standard of care (n=402) in patients requiring organ support in the ICU within 24 hours. Primary outcome: respiratory and cardiovascular organ support free days within 21 days.

The **median number of organ support-free days was less** in treatment vs. control - 10 in the tocilizumab group, 11 in the sarilumab group, and 0 in the control group. **Improved 90-day survival** for pooled IL-6 antagonist showed HR 1.61 (95% CI 1.25 to 2.08)

REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.

42

What about more than 2 immunomodulators?

- Combinations of 3 immunomodulators (e.g., dexamethasone plus baricitinib plus tocilizumab) have not been studied in clinical trials.
- Although some patients in the baricitinib arm of the RECOVERY trial also received tocilizumab, data from the study are insufficient to issue a recommendation.
- When both agents are used, there is a potential for greater risk of secondary infections.

43

Which patient is clinically indicated to receive IV tocilizumab (Actemra)? Select all that apply.

A. A patient with mild COVID-19, not requiring oxygen support but with risk factors for progression to severe COVID-19

B. B. A patient requiring low flow oxygen support that has remained steady at 2L/min but whose CRP has increased

C. A patient requiring low flow oxygen support with increasing oxygen requirements and whose CRP has increased

D. A patient requiring HFNC whose CRP remains elevated, but consistent

44

NIH Guideline Recommendations for Adults with COVID-19 Who Do Not Require Supplemental Oxygen

Non-hospitalized or Hospitalized for Reasons Other Than COVID-19

Preferred therapies in order of preferences:

Ritonavir-boosted nirmatrelvir (AIIa)[a-c]

Remdesivir (BIIa)[a,b,d]

Alternative therapy:

Molnupiravir (CIIa)[b,e,f]

Against use of dexamethasone or other systemic corticosteroids (AIIb)[g] unless these agents are being used to treat an underlying condition (AIII)

Hospitalized for COVID-19

Remdesivir[h] for patients who are:

- Immunocompromised (BIIb)
- At high risk for other reasons (BIII)

Against use of dexamethasone (AII) **or other systemic corticosteroids** (AIII)[i]

45

Patient Case: Jennifer – COVID-19 with No Supplemental Oxygen Requirement

CHIEF COMPLAINT
77-year-old female presents with right hip and thigh pain, obvious fracture deformity

HISTORY OF PRESENT ILLNESS
Presented to the ED after a fall on her driveway. Reported feeling weak with a headache 2 days prior that may have contributed to the fall. Sore throat and mild worsening of her baseline shortness of breath x 3 days. Tested positive for COVID-19 in the ED

MEDICAL HISTORY
Conditions – Hypertension, COPD, Rheumatoid arthritis, Diabetes mellitus
Medications – Adalimumab, Corticosteroids (chronic)

CLINICAL PRESENTATION

Vital Signs
Temp: 97.9°F
BMI: 30 kg/m^2
BP: 171/99 mmHg
HR: 90 bpm
RR: 18 BPM
SpO2: 95% on room air

Labs
AST: 33 U/L
ALT: 27 U/L
CRP: 8 mg/L
eGFR: 75 mL/min/1.73m^2
RT-PCR: positive for SARS-CoV-2

Radiology
Chest x-ray: increased lung volumes and diaphragmatic flattening normal heart size, no infiltrate/ effusion

Photo: https://ezadxdiarsm.exactdn.com/wp-content/uploads/2019/07/Karen-Kay-480x660.jpg?lossy=0&ssl=1

46

Patient Case: Jennifer – COVID-19 with No Supplemental Oxygen Requirement

ASSESSMENT AND PLAN
The patient has COVID-19 with a high risk for progression to severe disease
The patient was admitted to the hospital, with orthopedic consult

After being admitted, the following were administered
- IV fluids
- Pain control
- Remdesivir 200mg IV on Day 1 followed by remdesivir 100mg IV on Days 2 and 3 (3 days total duration)
- Dexamethasone NOT indicated as no supplemental oxygen

Photo: https://ezadxdiarsm.exactdn.com/wp-content/uploads/2019/07/Karen-Kay-480x660.jpg?lossy=0&ssl=1

47

NIH Guideline Recommendations for Adults with COVID-19 Who Require Supplemental Oxygen

Conventional Oxygen

Veklury + dexamethasone (BIIa)[a,b].

Patient receiving dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add

- **PO baricitinib** (BIIa) **or IV tocilizumab** (BIIa)

Alternative: **IV abatacept** (CIIa) or **IV infliximab** (CIIa)

HFNC OXYGEN or NIV

Dexamethasone (AI). If not already initiated promptly add 1 of the following immunomodulators:
- Preferred: **PO baricitinib** (AI)
- Preferred alternative: **IV tocilizumab** (BIIa)
- *Alternatives*: IV abatacept or IV infliximab (CIIa)

Add **remdesivir** in certain patients, including:
- Immunocompromised (BIIb)
- Evidence of ongoing viral replication (BIII)
- ≤ 10 days of symptoms (CIIa)

MV or ECMO

Dexamethasone (AI). If patient has not already received a second immunomodulator, promptly add:
- **PO baricitinib** (BIIa) or
- **IV tocilizumab** (BIIa)

Insufficient evidence for or against **remdesivir**

48

Patient Case: Jonah – COVID-19 Requiring Supplemental Oxygen

Photo: https://unsplash.com/s/photos/black-man

CHIEF COMPLAINT
61-year-old male presents with worsening shortness of breath, productive cough, malaise, and bilateral leg edema

MEDICAL HISTORY
COPD, tobacco use disorder (2 packs of cigarettes daily)

CLINICAL PRESENTATION
Physical Exam: no chest pain, chills, wheezing, or rales. In respiratory distress with use of accessory muscles of respiration.

Vital Signs	Labs	Radiology
Temp: 98.9°F	AST: 30 U/L	Chest x-ray:
BMI: 19.8 kg/m^2	ALT: 32 U/L	silhouette WNL,
HR: 77 bpm	BP: 129/75 mmHg	eGFR: 88.2 mL/min/1.73m^2
RR: 28 BPM	RT-PCR: positive for SARS-CoV-2	CT scan: negative PE
SpO2: 94% on room air	ABG hypercarbia,	Venous duplex: negative DVT

cardiomediastinal emphysema. detected. No acute pulm

49

Patient Case: Jonah – COVID-19 Requiring Supplemental Oxygen

Photo: https://unsplash.com/s/photos/black-man

ASSESSMENT AND PLAN
- The patient was diagnosed with COPD exacerbation due to COVID-19, with impending respiratory failure and started on 2L of oxygen via nasal canula
- He was admitted to the ICU.

The following were administered:
- Ipratropium bromide/albuterol
- Methylprednisolone 125 mg IV, followed by oral prednisone x 5 days for COPD exacerbation
- Remdesivir 200 mg IV on Day 1 followed by remdesivir IV on Day 2 – 5

50

Patient Case: Jonah – COVID-19 Requiring Supplemental Oxygen

Patient course:
On Day 2 the patient had increasing oxygen needs from 2L to 4L nasal canal and signs of systemic inflammation (CRP 45 mg/L)

The following was administered:
- IV tocilizumab 8mg/kg x 1

Photo: https://unsplash.com/s/photos/black-man

51

Special Populations

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.
https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

52

Pregnancy

Drug Name (in alphabetical order)	Pregnancy	Lactation
Baricitinib	**Recommended** in hospitalized patients, if indicated. Pregnant patients and their health care providers should jointly decide whether to use baricitinib during pregnancy, and the decision-making process should include a discussion of the potential risks and benefits.	Feeding breast milk **should be avoided** while taking baricitinib and for 4 days after the last dose. Lactation support should be provided during this time.[a]
Dexamethasone	**Recommended** in hospitalized patients, if indicated.	Should be offered to patients who qualify for this therapy. Breastfeeding can continue while a patient receives dexamethasone.

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.
https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

53

Pregnancy

Drug Name (in alphabetical order)	Pregnancy	Lactation
Molnupiravir	**Recommended against**, unless there are no other options and therapy is clearly indicated.	Breastfeeding **is not recommended** while a patient is taking molnupiravir and for 4 days after the last dose.[1] Lactation support should be provided during this time.[a]
Remdesivir	**Recommended**, if indicated.	Should be offered to patients who qualify for this therapy. Breastfeeding can continue while a patient receives remdesivir.
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	**Recommended**, if indicated.	Should be offered to patients who qualify for this therapy. Breastfeeding can continue while a patient receives ritonavir-boosted nirmatrelvir.
Tocilizumab	**Recommended** in hospitalized patients, if indicated. Pregnant patients and their health care providers should jointly decide whether to use tocilizumab during pregnancy, and the decision-making process should include a discussion of the potential risks and benefits.	Should be offered to patients who qualify for this therapy. Breastfeeding can continue while a patient receives tocilizumab.

54

Table 3c. Therapeutic Management of Hospitalized Children With COVID-19

Disease Severity	Panel's Recommendations
Hospitalized for COVID-19	For children aged ≥12 years admitted for COVID-19, use prophylactic anticoagulation unless contraindicated **(BIII)**.[a]
Does Not Require Supplemental Oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19[b] (especially those who are severely immunocompromised), consider using **remdesivir**[c] for children aged 12–17 years **(CIII)**. There is insufficient evidence for using remdesivir in children aged 28 days to <12 years and weighing ≥3 kg.
	For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression,[b] refer to Therapeutic Management of Nonhospitalized Children With COVID-19.
Requires Conventional Oxygen[d]	Use 1 of the following options: • **Remdesivir**[c] **(BIII)** • **Dexamethasone plus remdesivir**[c] for children with increasing oxygen needs, particularly adolescents **(BIII)**
Requires Oxygen Through High-Flow Device or NIV[e]	Use 1 of the following options: • **Dexamethasone (BIII)** • **Dexamethasone plus remdesivir**[c] **(BIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[f] or **tocilizumab** can be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Requires MV or ECMO[g]	**Dexamethasone**[g] **(AIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[f] or **tocilizumab** may be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.	

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

55

Management of Patients With COVID-19 Who Are Immunocompromised

- Clinicians should consult with the appropriate specialists when making decisions about stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19.
- When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the severity of COVID-19; and the potential for drug-drug interactions, overlapping toxicities, and secondary infections.
- For nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population **(AIII)**. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.
- For most hospitalized patients with severe or critical COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations recommended for the general population **(AIII)**. For more information, see Therapeutic Management of Hospitalized Adults With COVID-19.
- For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication, the optimal management is unknown. The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:
  - Longer and/or additional courses of ritonavir-boosted nirmatrelvir (Paxlovid)
  - Longer and/or additional courses of remdesivir
  - High-titer COVID-19 convalescent plasma from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

56

COVID-19 Convalescent Plasma

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma (CCP) for the treatment of COVID-19 in nonhospitalized patients who are immunocompromised.

The FDA issued an Emergency Use Authorization that allows the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized or hospitalized patients who have immunosuppressive disease or are receiving immunosuppressive treatment.[62] However, the evidence generated from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 is conflicting; these trials only enrolled a small number of patients who were immunocompromised.[63-66]

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.
https://www.ncbi.nlm.nih.gov/books/NBK570371/pdf/Bookshelf_NBK570371.pdf

57

Pre-exposure Prophylaxis (PrEP) for COVID-19

58

Pemivibart (Pemgarda™)

- Monoclonal antibody that targets SARS-CoV-2 spike protein receptor binding domain, inhibiting the attachment of SARS-CoV-2 virus to human ACE2 receptors
- Emergency Use Authorization (EUA) by FDA for PrEP in adults and adolescents (age 12 and older weighing at least 40kg) who are:
  - **Not currently infected with SARS-CoV-2**
  - **Have not had a known recent exposure** to an individual infected with SARS-CoV-2
  - **Have moderate to severe immune compromise** due to a medical condition or receipt of an immunosuppressive medication and unlikely to mount an adequate immune response to COVID-19 vacation

59

Pemivibart (Pemgarda™)

Key Considerations

- Administer via IV infusion over 60 minutes
- Repeat doses are recommended every three months to maintain protective antibody levels
- Boxed warning for anaphylaxis. Other potential ADE include infusion related hypersensitivity, URTI, fatigue, headache, and nausea.

60

Pipeline Agent – Ensitrelvir

- Similar class to nirmatrelvir in Paxlovid, targets main protease of SARS-CoV-2, essential for viral replication
- Marketing under Xocova in Japan, approved for mild to moderate COVID-19
- Late-Breaking CROI 2025: SCORPIO-PEP demonstrated statistically significant reduction (67%) in the risk of COVID-19, meeting e.g., primary endpoint, in uninfected individuals treated AFTER exposure, compared to placebo at day 10. In trial, given within 72 hours (3 days).
- Currently there are no approved medicine to prevent COVID-19 in people who have been exposed to a person with SARS-CoV-2 infection
- **Granted FDA Fast Track designation in 2024 for post-exposure prophylaxis**.
- Potential to consider for close contacts (e.g., household contacts, LTCF, nursing home residents).
- Logistical factors (e.g., timely identification and access, awareness and education, patient willingness)

https://www.shionogi.com/us/en/news/2025/03/late-breaking-at-croi-2025-scorpio-pep-phase-3-trial-ensitrelvir-is-the-first-and-only-covid-19-oral-antiviral-to-demonstrate-prevention-of-covid-19-as-post-exposure-prophylaxis.html?utm_source=chatgpt.com

61

Thank you

62