AETC AIDS Education & Training Center Program Southeast

Nirmatrelvir/ritonavir for COVID-19

Test, Treat and Therapeutic Updates

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Learning Objectives

- Describe the current evidence and therapeutic considerations for the use of nirmatrelvir/ritonavir to treat COVID-19
- Discuss important drug-drug interactions when prescribing nirmatrelvir/ritonavir for COVID-19
- Discuss new laws and regulations related to test and treat and pharmacists role in expanding nirmatrelvir/ritonavir uptake

Disclosures

- The activity planners and speakers do not have any financial relationships with commercial entities to disclose.
- The speakers will not discuss any off-label use or investigational product during the program.
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

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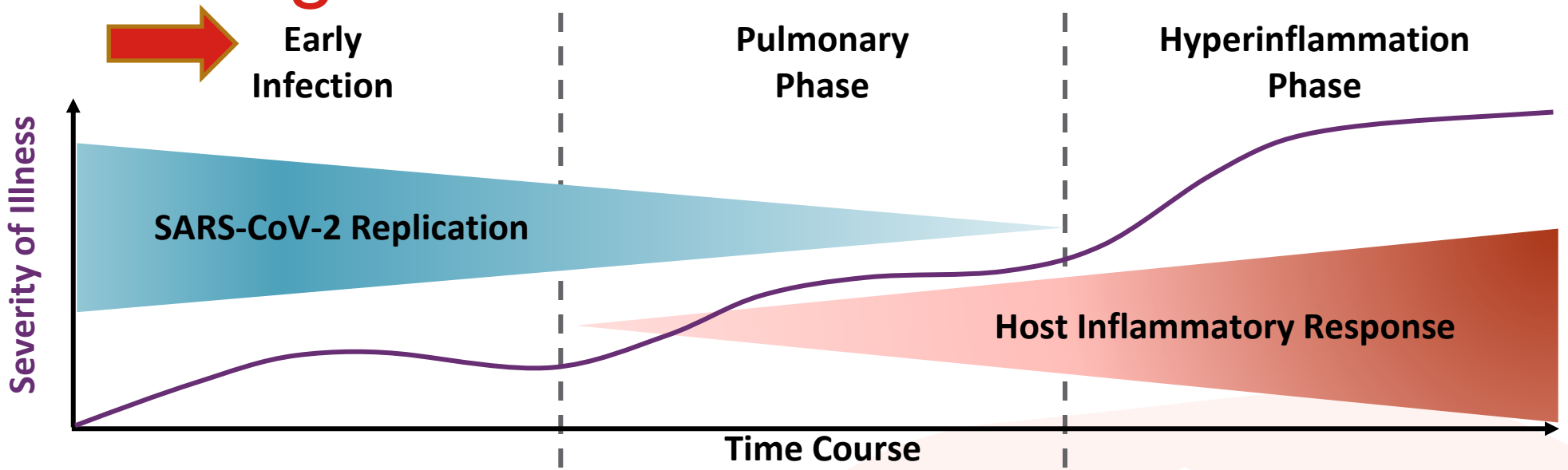
Introduction

COVID-19 Infection

- The virus is named SARS-CoV-2, which causes the illness COVID-19
- The estimated **incubation period** for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days
  - This represents the time from when you were exposed to the virus to the time you start to show symptoms
  - Some experts say certain variants may have shorter incubation periods
- Timely diagnosis is important, as current antiviral therapeutics work best when initiated within a few days

Benefit of Therapeutic Classes Dictated by SARS-CoV-2 Pathogenesis



Clinical Signs/ Symptoms	Lymphopenia, mild constitutional symptoms, fever >99.6°F, dry cough	Shortness of breath ± hypoxia, abnormal chest imaging, transaminitis, low-normal procalcitonin	ARDS, SIRS/shock, cardiac failure; elevated inflammatory markers, troponin, and NT-proBNP
Treatment Goals	Reduce onward transmission	Reduce progression/ hospitalization	Reduce morbidity/ mortality
	Enhance immunity; use antivirals	Dampen immunopathogenesis, coagulation	

NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated December 16, 2021.
Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

COVID-19 and Outpatient Options

First Line	Nirmatrelvir/ritonavir oral x 5 days
Second Line	Remdesivir IV x 3 days
Alternative therapy	Molnupiravir oral x 5 days
	Bebtelovimab IV once

Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate.

COVID-19 and Inpatient Options

- Remdesivir
- Dexamethasone
- Baricitinib
- Tocilizumab

In Vitro Susceptibility Based on Subvariants

Subvariant	Bebtelovimab	Tixagevimab+ Cilgavimab	*Imdevimab+ Casirivimab*
Reference	2.5	6.3	3.4
BA.1	5.8	351.1	>10,000
BA 1.1	3.9	1296.8	>10,000
BA. 2	3.3	34.6	835.1
BA. 2.12.1	4.0	38.1	452.7
BA.4	2.9	37.8	459.1
BA. 5	3.3	192.5	1093.1

Numbers represent ng/mL concentrations required for In-vitro neutralizing ability against the subvariants tested

- Bebtelovimab is currently the only mab available for acute infection
- Tixagevimab+ Cilgavimab is for prevention in specific immunocompromised patients

Table recreated from: Table 1 in N Engl J Med. 2022 Jul 20

N Engl J Med. 2022 Jul 20. doi: 10.1056/NEJMc2207519.

In Vitro Susceptibility Based on Subvariants

Subvariant	Remdesivir	Molnupiravir	Nirmatrelvir
Reference	1.7	2.8	**2.7**
BA.1	1.9	7.5	**4.8**
BA 1.1	2.0	6.0	**3.9**
BA. 2	5.9	8.7	**6.9**
BA. 2.12.1	0.5	3.2	**1.8**
BA.4	1.2	3.3	**2.9**
BA. 5	2.0	4.1	**4.4**

Drug concentrations in μmol, susceptibility measured as in vitro 50% inhibitory concentration (IC_{50})

Table recreated from: Table 1 in N Engl J Med. 2022 Jul 20

N Engl J Med. 2022 Jul 20. doi: 10.1056/NEJMc2207519.

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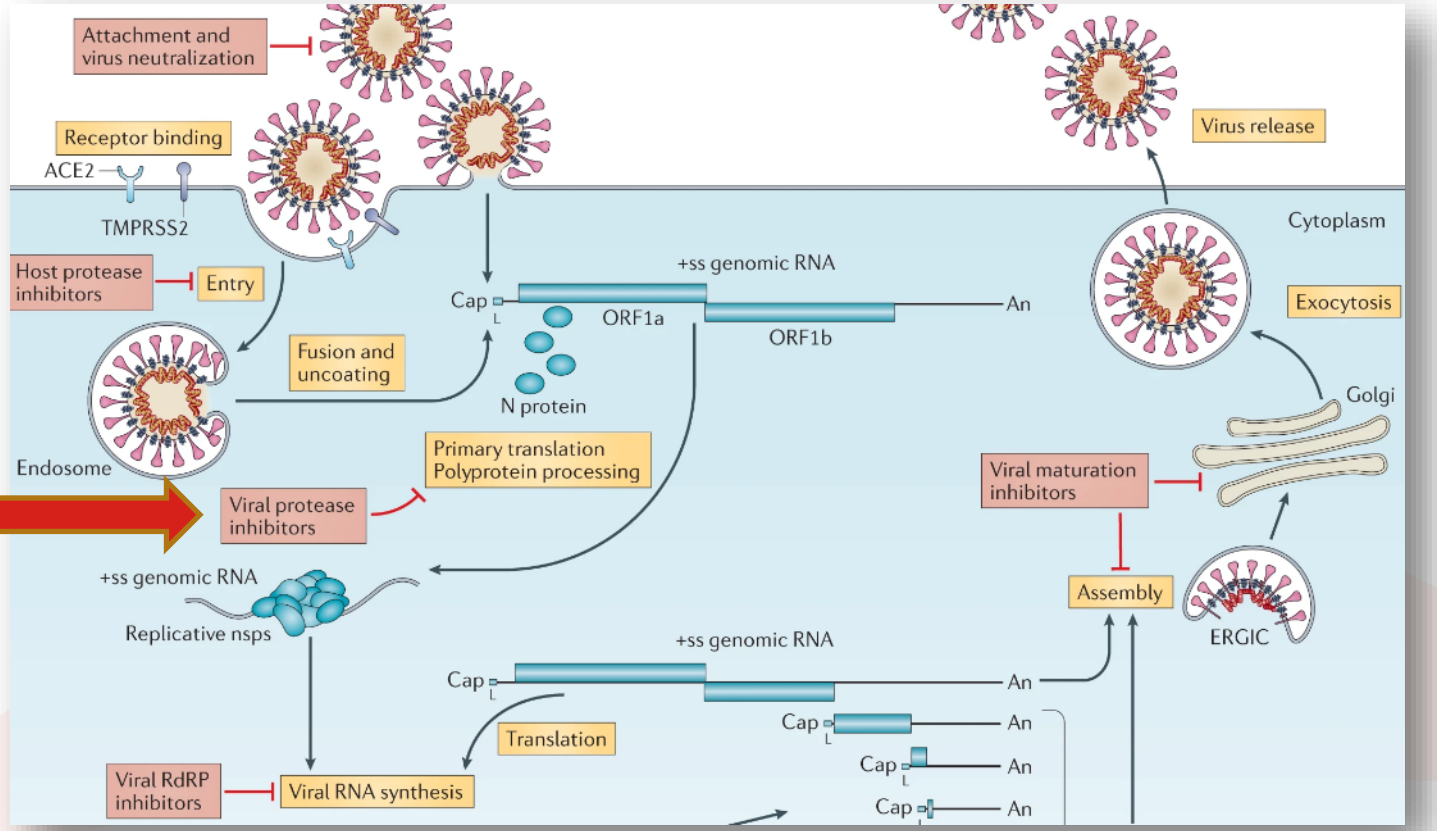
Therapeutic considerations for the use of nirmatrelvir/ritonavir to treat COVID-19

Nirmatrelvir

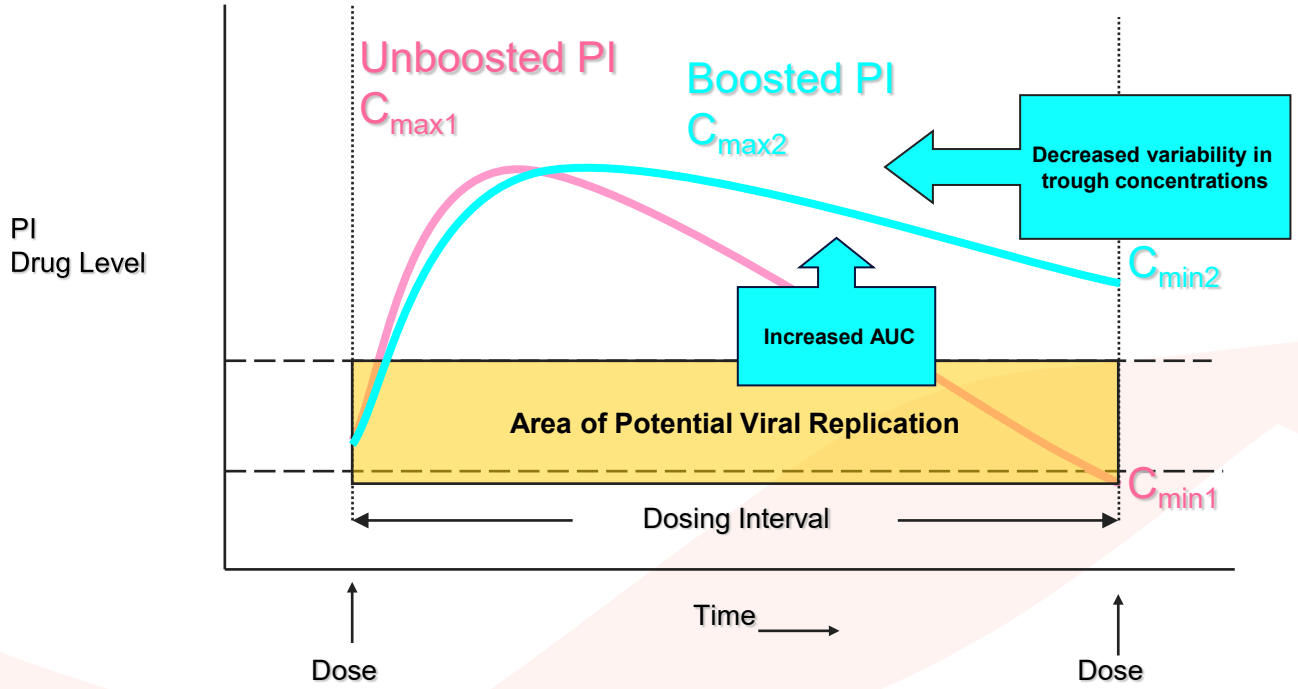
Mechanism of action:

- Protease inhibitor (Mpro) with booster. Inhibition of SARS-CoV-2 main protease renders it incapable of processing polyprotein precursors, preventing viral replication



V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol. 2021 Mar;19(3):155-170. doi: 10.1038/s41579-020-00468-6.

Boosting a Protease Inhibitor (PI) With Ritonavir



FDA EUA for Nirmatrelvir + Ritonavir

"authorized the emergency use of nirmatrelvir tablets and ritonavir tablets for the ***treatment of mild-to-moderate COVID-19 in adults and pediatric patients*** *(12 yrs or older, weighing at least 40 kg [88 lbs]) with* ***positive results of direct SARS-CoV-2 viral testing****, and* ***who are at high risk for progression to severe COVID-19****, including hospitalization or death."*

- Nirmatrelvir must be coadministered with ritonavir
- Initiate nirmatrelvir + ritonavir treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset
- **Dosing:**
  - 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days
  - Dose reductions must be made for patients with moderate renal impairment

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-receives-us-fda-emergency-use-authorization-novel Nirmatrelvir plus Ritonavir. EUA Fact Sheet for Healthcare Providers. Last updated December 22, 2021.

Slide credit: clinicaloptions.com

Risk factors of COVID19 severe disease

Are at increased risk of severe illness:

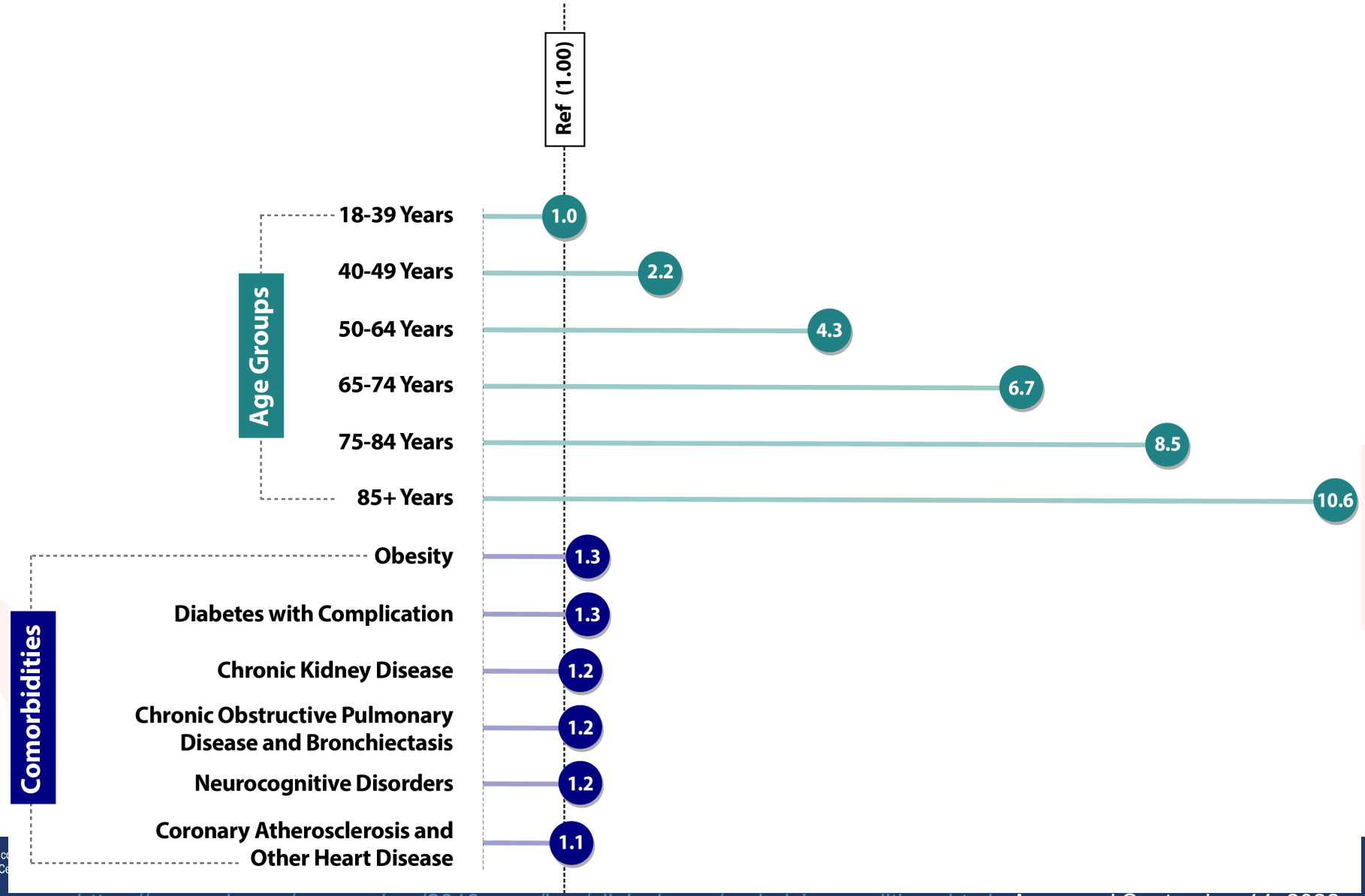
- **Age**
- Cancer
- Chronic kidney disease
- Chronic lung diseases (COPD, Cystic fibrosis, Asthma, interstitial lung disease, Pulmonary fibrosis, PE, Pulmonary hypertension)
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Dementia
- Mental health disorders (depression and schizophrenia)
- Solid organ or stem cell transplant

Increased Risk continued:

- Diabetes mellitus type 1 or 2
- Cerebrovascular disease or history of stroke
- HIV infection
- Tuberculosis
- Use of corticosteroids, or use of other immunosuppressive medicines
- Liver disease
- Obesity (BMI > 30 kg/m2)
- Pregnancy or recent pregnancy
- Primary Immunodeficiencies
- Smoking (including former smokers)
- Disabilities
- Physical inactivity

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html Accessed September 14, 2022.

COVID-19 Death Risk Ratio (RR) for Select Age Groups and Comorbid Conditions



https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html Accessed September 14, 2022.

Side effects reported with nirmatrelvir/ritonavir

- dysgeusia (an altered or impaired sense of taste)
- diarrhea
- increased blood pressure
- muscle aches
- abdominal pain
- nausea

Hammond. N Engl J Med 2022;386:1397-408. DOI: 10.1056/NEJMoa2118542.,
https://www.fda.gov/media/155050/download

Dose reduction for renal impairment

- Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min):
  - 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
- Not recommended for eGFR<30mL/min

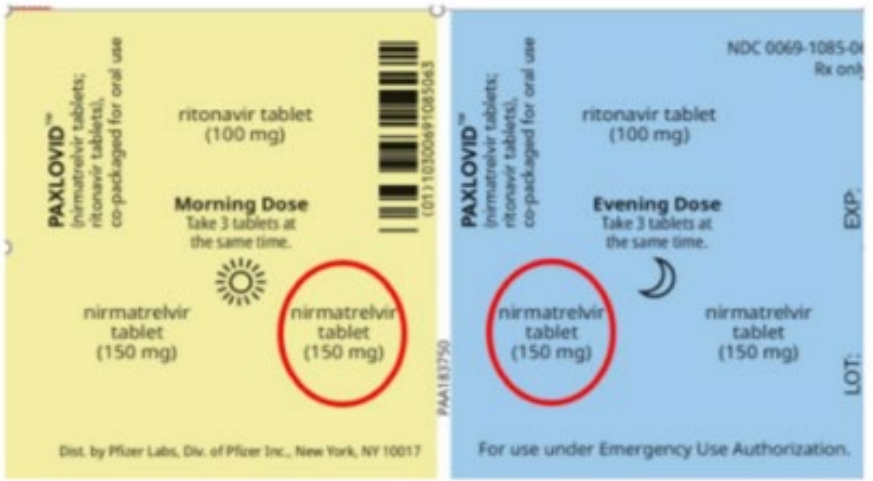
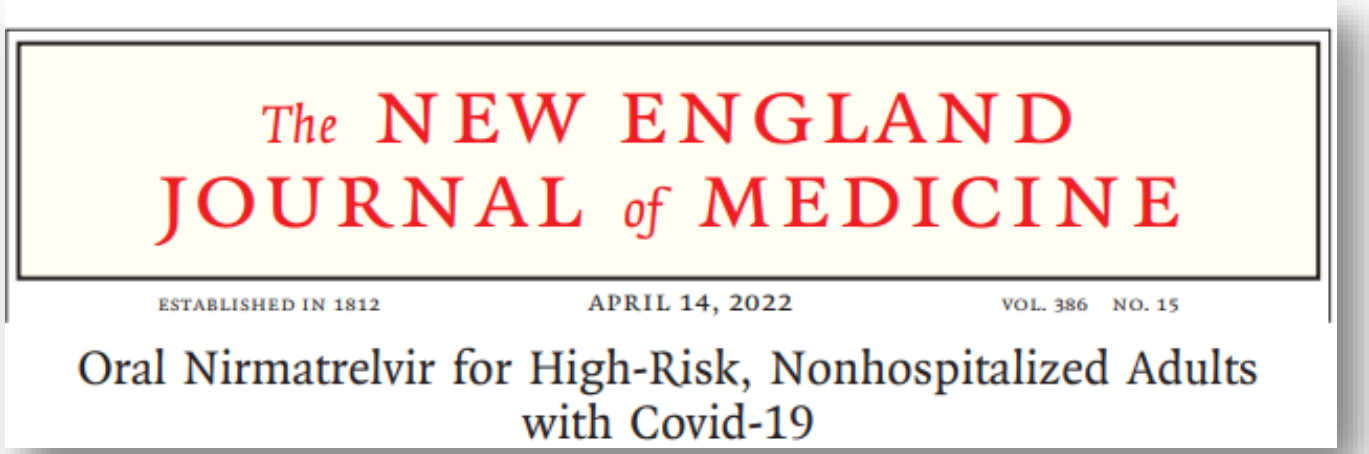


Figure 1. The red ovals in the image are where the nirmatrelvir tablets should be removed prior to dispensing Paxlovid to patients with moderate renal impairment; then, a pre-printed sticker (**Figure 2**) with dosing instructions, should be placed over the empty blisters.

Figure 2. A pre-printed sticker with dosing instructions (provided by the manufacturer) is placed over the empty blisters where the nirmatrelvir tablets were removed for patients with moderate renal impairment.

https://www.fda.gov/media/155050/download

EPIC-HR



- **E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients
- N=2246 patients
- Symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe COVID
- Patients had mild to moderate disease
- Included if confirmed SARS-CoV-2 infection and symptom onset no more than 5 days before randomization
- All had at least one characteristic or coexisting condition associated with high risk of progression to severe COVID
  - 1370 patients (61.0%) had two or more such characteristics or coexisting conditions

Hammond. N Engl J Med 2022;386:1397-408. DOI: 10.1056/NEJMoa2118542.

EPIC-HR: Day 28 Final Efficacy Analysis

	Started by Day 3			Started by Day 5		
Outcome, n (%)	**Nirmatrelvir + RTV (n = 697)**	**Placebo (n = 682)**	**P Value**	**Nirmatrelvir + RTV (n = 1039)**	**Placebo (n = 1046)**	**P Value**
Hospitalization or death	5 (0.7)	44 (6.5)	<.0001	8 (0.8)	66 (6.3)	<.0001
Deaths	0	9 (1.3)	<.0001	0	12 (1.1)	<.0001

- **Reduced risk of hospitalization or death by 89%** (*P* = .001) when started within 3 days of symptom onset (88% when started within 5 days)
- Safety analysis: fewer serious AEs and study drug discontinuations with nirmatrelvir + RTV vs placebo (1.6% vs 6.6% and 2.1% vs 4.2%, respectively)
- Owing to positive results, DSMB stopped recruitment early (initially planned 3000 participants)

Hammond. N Engl J Med 2022;386:1397-408. DOI: 10.1056/NEJMoa2118542.

EPIC-SR

- EPIC-SR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **S**tandard-**R**isk Patients)
  - ≥1 characteristic or underlying medical condition associated with increased risk of developing severe illness from COVID-19 **and** fully vaccinated
    - Or
  - Unvaccinated adults who were at standard risk (i.e., low risk of hospitalization or death)

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting

EPIC-SR- Interim Results

- Analysis at 80% of enrolled patients
  - No difference in the primary endpoint (self-reported, sustained alleviation of all symptoms for four consecutive days)
- For the secondary endpoint of hospitalization or death
  - Nirmatrelvir/ritonavir: 0.9% were hospitalized (5/576 hospitalized, no deaths)
  - Placebo:1.8% were hospitalized (10/569 hospitalized, 1 death)
    - non-significant 51% relative risk reduction
  - A sub-group analysis of 721 vaccinated adults with at least one risk factor for progression to severe COVID-19 (treatment arm: 3/361; placebo: 7/360)
    - **non-significant 57% relative risk reduction** in hospitalization or death

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-reports-additional-data-paxlovidtm-supporting

Future research efforts

- The FDA has requested that Pfizer study a longer course for patients with rebound symptoms
  - Anticipated study completed by September 2023
- Pfizer statement on further research efforts
  - “The company will focus efforts on generating further data on PAXLOVID in vulnerable populations, including longer treatment durations in immunocompromised individuals, as well as exploring other clinical development opportunities, such as its potential use in hospitalized patients with severe disease.”

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Important drug-drug interactions when prescribing nirmatrelvir/ritonavir for COVID-19

Contraindications

History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components.

Contraindications related to drug-drug interactions

- Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.
- Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Nirmatrelvir Plus Ritonavir

- Ritonavir is a potent CYP3A inhibitor
- Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir (which allows for twice daily dosing)
- Many medications are substrates or are metabolized by CYP3A, resulting in significant drug-drug interactions

Nirmatrelvir Plus Ritonavir: CYP3A Metabolism

Select Recommendations	
Contraindicated	**Use With Caution**
↑ alfuzosin ↑ piroxicam ↑ ranolazine ↑ amiodarone ↑ anti-cancer drugs ↑ rivaroxaban ↑ colchicine ↑ glecaprevir/pibrentasvir ↑ salmeterol ↑ sildenafil ↑ midazolam ↓ voriconazole	↑↓ warfarin (monitor INR) ↓ bupropion ↑ trazadone ↑ anti-HIV protease Inhibitor ↓ raltegravir ↑ clarithromycin/erythromycin ↑ rifabutin ↑ quetiapine ↑ digoxin ↓ ethinyl estradiol (use add'l contraception) ↑ Immunosuppressants ↑ corticosteroid ↑ fentanyl ↓ methadone
Phenytoin, carbamazepine, rifampin, St John's wort all ↓ nirmatrelvir + ritonavir	*Hold if giving to avoid increase: lovastatin, simvastatin, atorvastatin, rosuvastatin, bosentan*

- Review the patient's medications and supplements
- Nirmatrelvir + ritonavir = CYP3A inhibitor, so may increase levels of other drugs
- When used with CYP3A inducers, may not achieve adequate levels of nirmatrelvir

Clinically Significant Drug Interactions Between Nirmatrelvir/Ritonavir and Antiretrovirals

- Nirmatrelvir/Ritonavir Effect on Antiretroviral Concentrations
  - ↑ efavirenz
  - ↑ maraviroc
  - ↑ nevirapine
  - ↑ bictegravir
  - ↔ emtricitabine
  - ↑ tenofovir
  - ↑ atazanavir
  - ↑ darunavir
- Main course of management is to monitor for adverse effects due to higher concentrations of antiretrovirals

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COVID-19 Viral Rebound

COVID-19 Rebound After Nirmatrelvir/ritonavir Treatment

- Relapse or rebound occurs
- Patients are contagious and documented transmissions have occurred during relapse
- NIH guidelines state that longer treatment courses of ritonavir-boosted nirmatrelvir are **not authorized** based on the current EUA, and there are insufficient data on the efficacy of administering a second course

Characterization of Symptom Rebound in a Mayo Clinic Cohort

- Retrospective review of patients at Mayo Clinic Rochester who received nirmatrelvir plus ritonavir for mild to moderate SARS-Cov-2 infection
  - Median age: 63 yr; 56% female; 93% fully vaccinated
  - Time from positive SARS-CoV-2 test to nirmatrelvir plus ritonavir prescription: 1 day (IQR: 1-2 days)
- Rebound defined as recurrence of COVID-19 symptoms following completion of 5 days of nirmatrelvir plus ritonavir
- 4 of 483 patients (0.8%) experienced rebound
  - All were fully vaccinated
- Median time to rebound after nirmatrelvir plus ritonavir treatment: 9 days (IQR: 7.0-14.5 days)
- All resolved **without** hospitalization or additional COVID-19–directed therapy

Raganath. Clin Infect Dis. 2022;[Epub].

Characterization of Symptom Rebound Following Nirmatrelvir Plus Ritonavir Treatment for COVID-19

- Analysis of 7 patients identified through the Mass General Brigham health system or upon referral from treating providers with recurrent symptoms following nirmatrelvir plus ritonavir treatment
- **No known resistance associated mutations identified**
- 92% concordance between antigen and viral culture testing
- Positive cultures have implications for infectiousness

Parameter	All Patients (N = 7)
Median time to symptom recurrence, days ▪ After initial positive test ▪ After completion of nirmatrelvir + ritonavir course	 9 4
Median viral load, log_{10} copies/mL (range)	6.1 (4.2-7.3)
Duration of detectable viral load, days (range) ▪ After initial PCR test ▪ After initiation of nirmatrelvir + ritonavir	 17 (14-20) 12 (9-16)
Culturable virus present at enrollment, n (%)	3 (43)
Duration of positive cultures among patients (n = 3) with culturable virus, days ▪ After time of initial PCR test ▪ After completion of nirmatrelvir + ritonavir course	 10, 16, 16 5, 11, 11

Boucau. Clin Infect Dis. 2022;[Epub]. https://doi.org/10.1093/cid/ciac512

Virologic, Immunologic Characterization of Variant Isolated From Patient With COVID-19 Recurrence After Nirmatrelvir Plus Ritonavir

- SARS-CoV-2 BA.2 PRSD01 was isolated from a patient who developed rebound symptoms, high viral shedding, and culturable virus 5 days after treatment with nirmatrelvir plus ritonavir
- **No sequence differences** from a BA.2 reference were noted
- IC_{50} of nirmatrelvir against BA.2 PRSD01 was 1.7- to 2.0-fold lower vs other strains
- Plasma neutralizing antibody response was similar between the patient with rebound and 2 controls
  - Implies humoral immunity was not impaired by early treatment
- Development of nirmatrelvir resistance and absence of neutralizing antibody **were unlikely causes of rebound**

Carlin. Clin Infect Dis. 2022;[Epub]. doi: 10.1093/cid/ciac496.

Immune Responses Appear Intact During Rebound

- Patients (N = 7) with rebound symptoms, 6 treated with nirmatrelvir plus ritonavir
  - 1 of 7 culture positive during rebound
- Omicron-specific neutralizing antibodies and T-cell responses elevated during rebound
- No resistance mutations detected
- **Rebound is not easily explained by impaired immunity nor resistance mutations**

Omicron Spike Surrogate Viral Neutralization Test

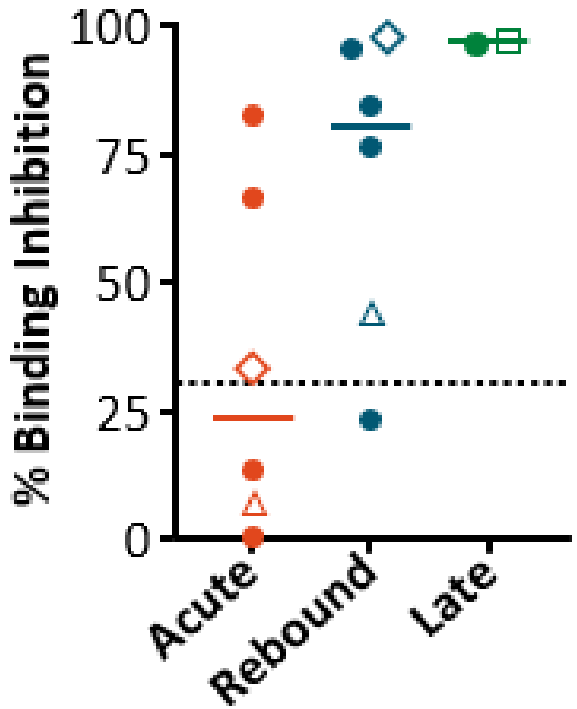

Figure legend: Median percent binding inhibition: lines; individual results: points; open diamond and triangle: longitudinal patients 1 and 2; open square: COVID-19 rebound patient not receiving nirmatrelvir plus ritonavir; dotted line: positive result cutoff

Epling. medRxiv preprint. 2022;doi: 10.1101/2022.06.16.22276392. Note: this study has not been peer reviewed.

Questions remain

- What is the cause of the viral rebound?
- Are there patient specific characteristics that make them more likely to have rebound?
- Would a longer treatment course benefit certain patients? (and who are those patients)
- Will treatment with nirmatrelvir/ritonavir reduce the risk for long COVID, or other prolonged post-infectious symptoms?

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Laws and regulations for prescribing

FDA Authorizes Pharmacists to Prescribe Nirmatrelvir Plus Ritonavir

Goal is to expand access to timely treatment

- Nirmatrelvir/ritonavir must be initiated within 5 days of COVID-19 symptom onset

Pharmacists should refer patients to another authorized prescriber if:

- Unable to assess renal and hepatic function
- Drug interaction assessment is not possible
- A medication modification needs to be made because of an interaction
- Nirmatrelvir/ritonavir is not an appropriate therapeutic option

FDA Authorizes Pharmacists to Prescribe Paxlovid with Certain Limitations

Electronic or printed health records <12 months old, including the most recent laboratory blood work for the state-licensed pharmacist to review for kidney or liver problems. *State-licensed pharmacists could also receive this information through a consult with the patient's health care provider.*

List of all medications they are taking, including OTC medications so the state-licensed pharmacist can screen for drug-drug interactions.

over-the-counter: OTC

https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pharmacists-prescribe-paxlovid-certain-limitations

What Physicians Can Expect

- Physicians may receive inquiries from pharmacists requesting patient health records
  - Including information regarding renal and hepatic function and medication history
  - Patients may also request their health records to provide to their pharmacist
- Physicians are encouraged to provide timely consultation, so patients have the ability to access treatment

PATIENT CASE

Patient Case example

- A 65-year-old female with a BMI of 24, no smoking history and no co-morbidities presents to her primary care doctor with early symptoms of COVID-19 after a known exposure. She is vaccinated and boosted. She tests positive and today is day 3 of her symptoms.
- Medications: none
- Do you recommend nirmatrelvir/ritonavir?

References

- NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated August 8, 2022
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Questions?