Outpatient COVID-19 Therapeutics in People with HIV

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Disclaimer

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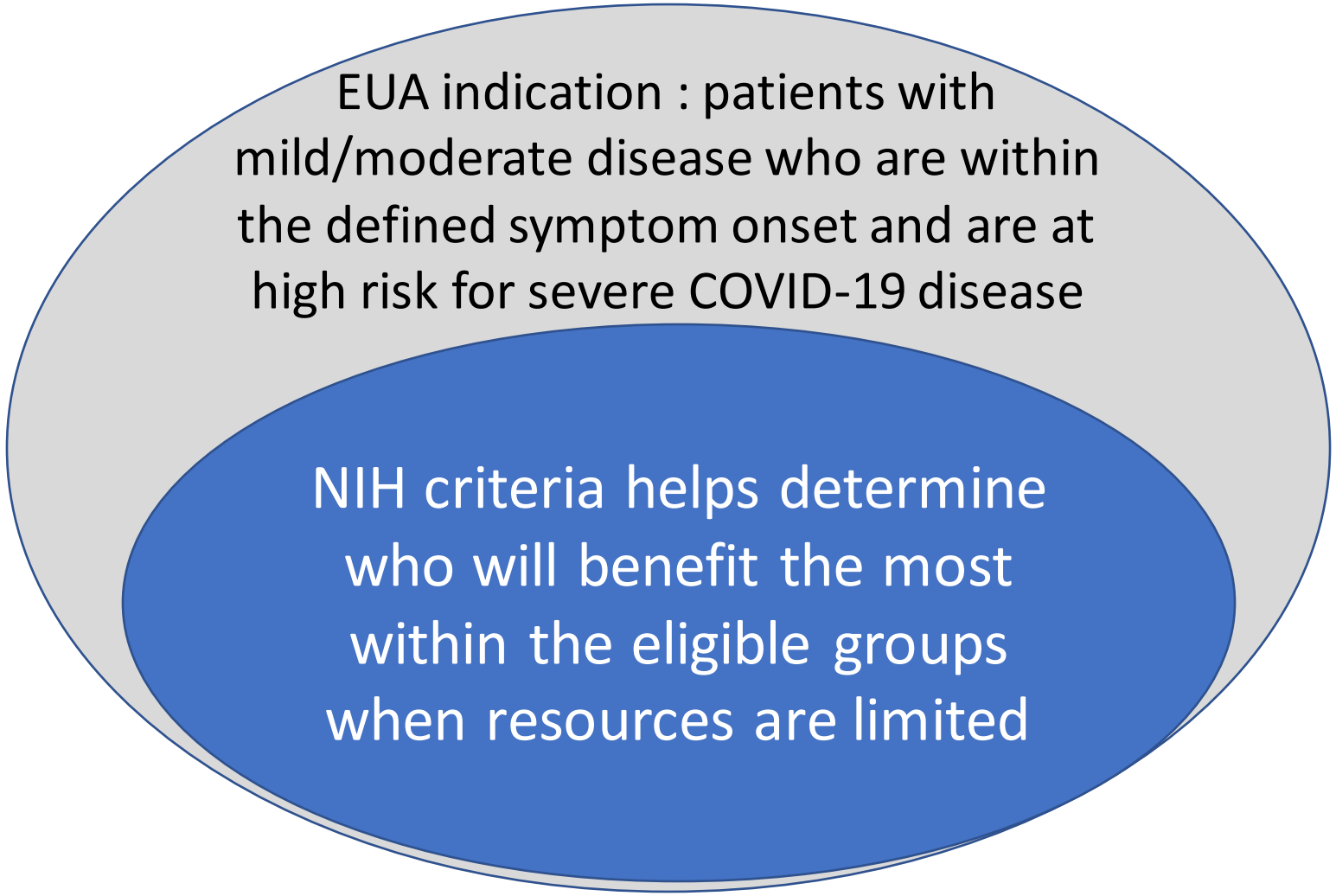
AETC AIDS Education & Training Center Program Mountain West

Learning Objectives

- Review available outpatient therapeutics for COVID-19 disease in people with HIV
- Review eligibility and contraindications to therapy
- Review current workflows for ordering therapy
- Review treatment for preventing COVID-19 disease

Therapy Timeline

EUA indication vs NIH Tiers



Tier 1

- **Immunocompromised individuals** not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status

or

- **Unvaccinated individuals** at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).

https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/

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NIH Tiers – prioritization

Tier 2

Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)

Tier 3

Vaccinated individuals at high risk of severe disease (**anyone aged ≥75 years or anyone aged ≥65 years** with clinical risk factors)

Tier 4

Vaccinated individuals at risk of severe disease (**anyone aged ≥65 years or anyone aged <65 years** with clinical risk factors)

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Case – a patient with well controlled HIV

47-yr-old woman with HIV (CD4 count 650 and HIV VL UD) calls your office after testing positive by home rapid Ag test for COVID-19 . She endorses a new cough, fever, and headache and has been feeling short of breath when walking around their apartment.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: none; BMI = 25

Symptoms started 2 days ago

Medication list: elvitegravir/cobicistat/F/TAF

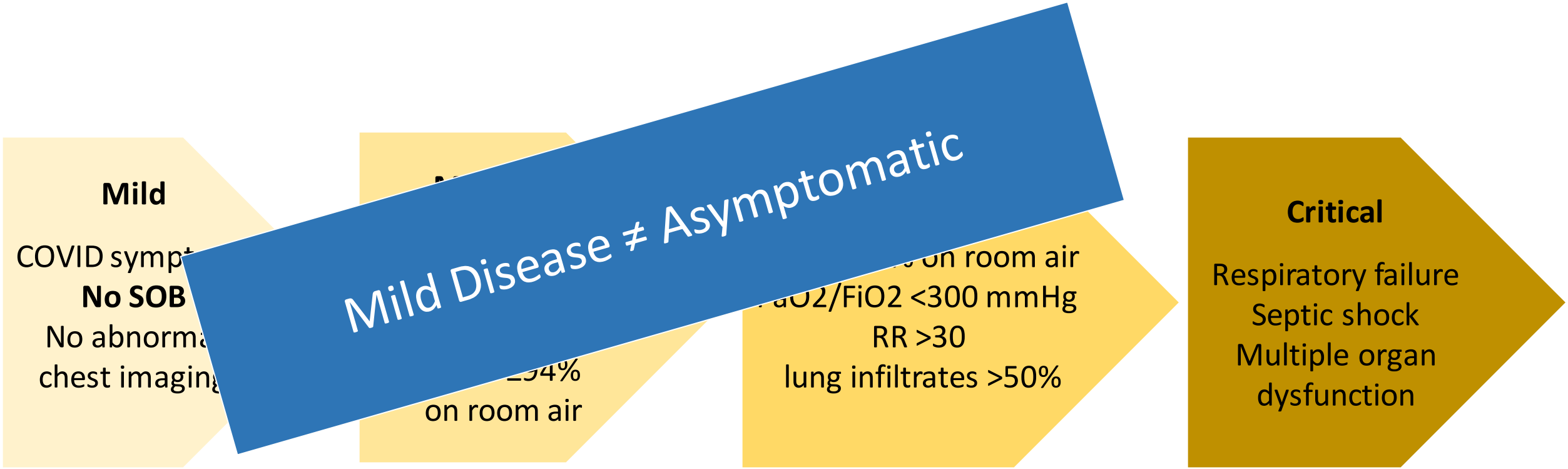
What is this patient's disease severity at presentation?

What are the risk factors for severe COVID-19 ?

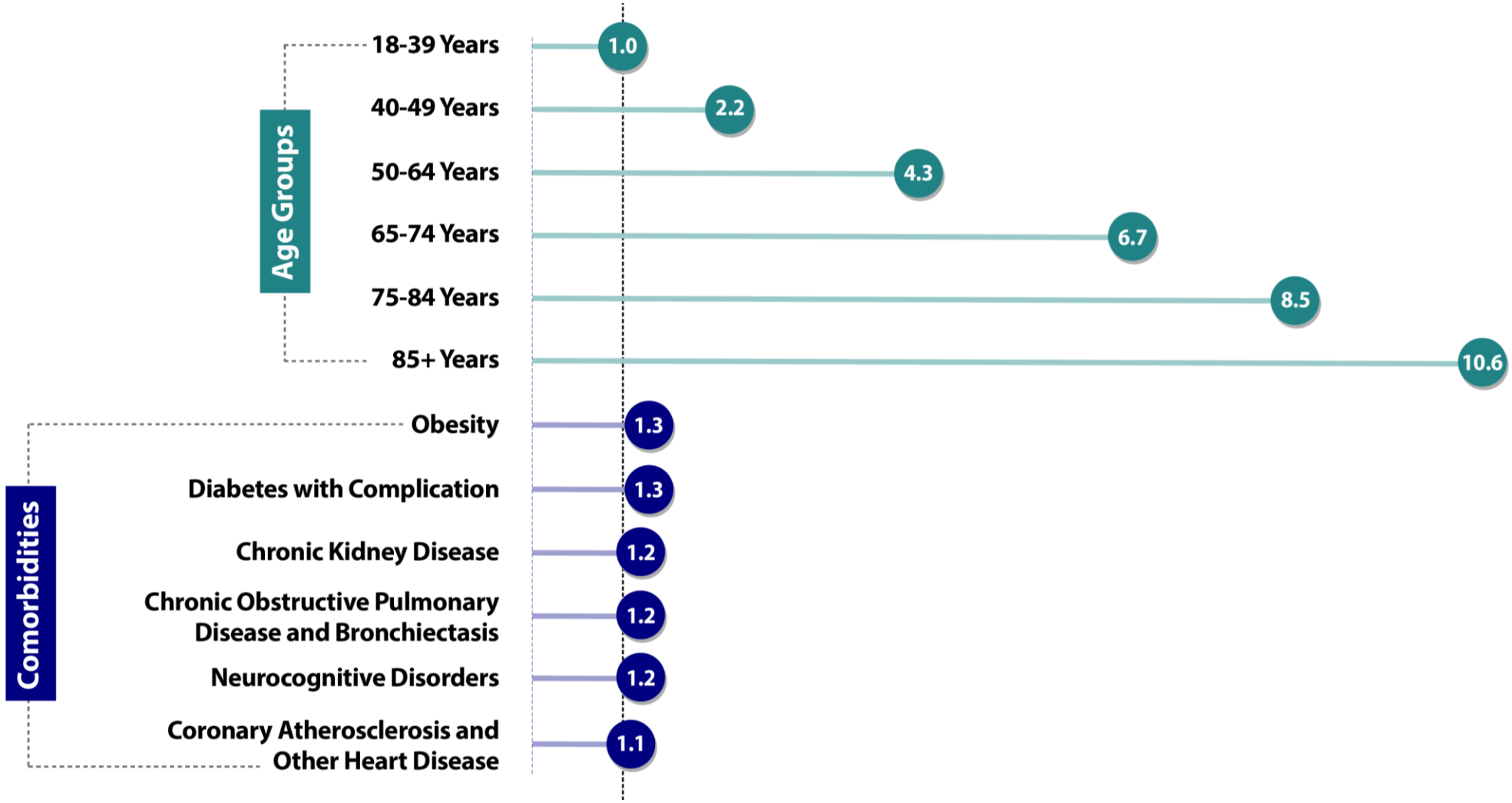
Does this patient need therapy?

Disease Severity Classification

NIH Criteria



Risk Factors for Disease Progression



Underlying Medical Conditions. CDC 2022

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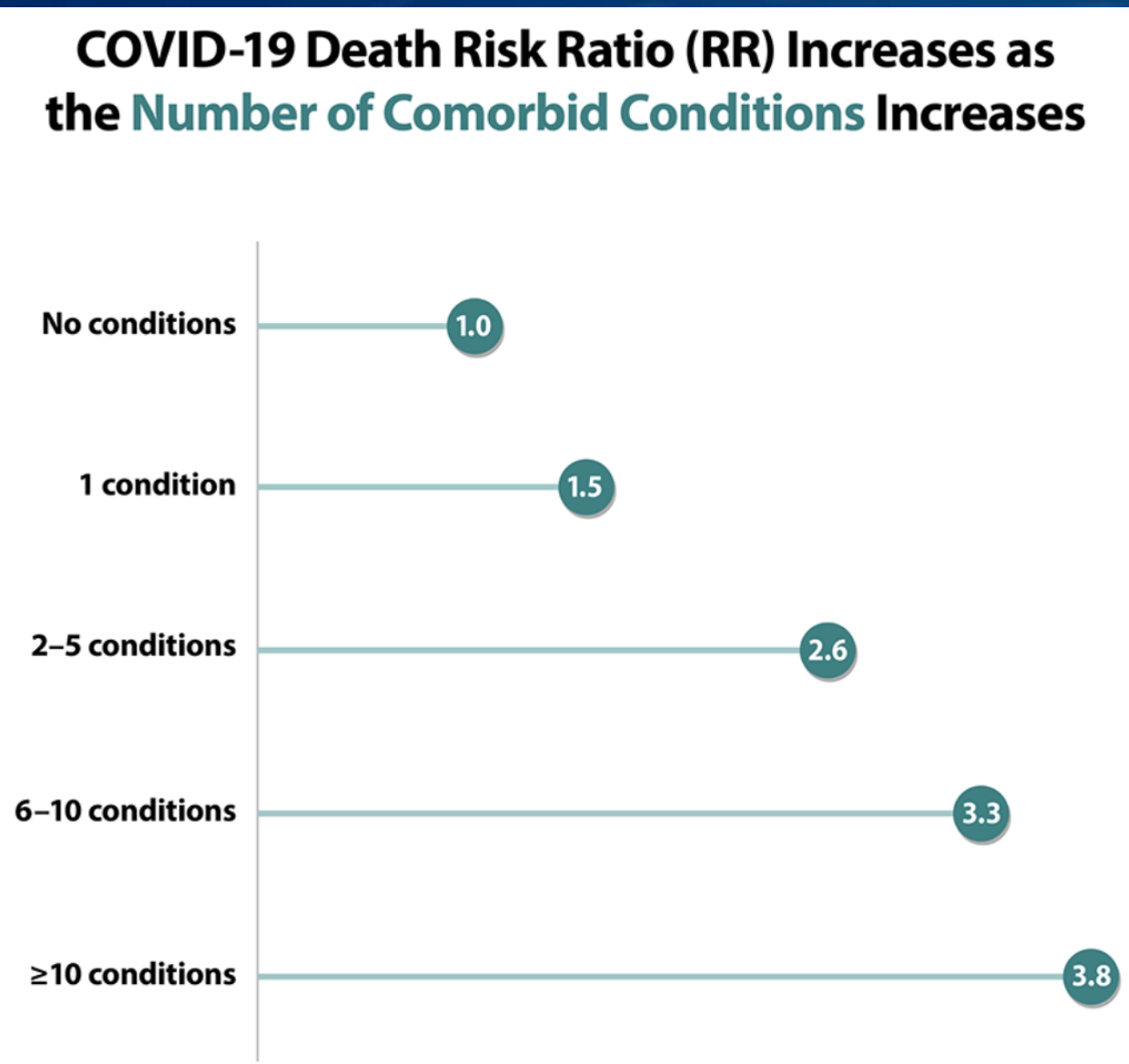
Other factors

- Immunosuppression
- Cancer
- Pregnancy/ recent Pregnancy
- Polysubstance abuse
- Obesity (BMI ≥ 30)
- Chronic Liver Disease

See CDC website for complete list



https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

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Case – a patient with no Co-morbidities

47-yr-old woman with HIV (CD4 count 650 and HIV VL UD) calls your office after testing positive by home rapid Ag test for COVID-19 . She endorses a new cough, fever, and headache and has been feeling short of breath when walking around their apartment.

Pulse Ox at home: 97%

COVID-19: vax and boosted

PMH: none; BMI = 25

Symptoms started 2 days ago

Medication list: elvitegravir/cobicistat/F/TAF

What is this patient's disease severity at presentation?

Mild-moderate

What are the risk factors for severe COVID-19 ?

HIV

Is the patient eligible for treatment?

Yes

NIH COVID-19 Treatment Guidelines

Therapeutic Management of Non-hospitalized Adults With COVID-19

Does Not Require Hospitalization or Supplemental Oxygen

All patients should be offered symptomatic management **(AIII)**.

For patients who are at high risk of progressing to severe COVID-19 (treatments are listed in order of preference based on efficacy and convivence of use):

- **Ritonavir-boosted nirmatrelvir**
- **Remdesivir**
- **Bebtelovimab**
- **Molnupiravir**

The panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.

Therapeutic goal: AVOID hospitalization and death

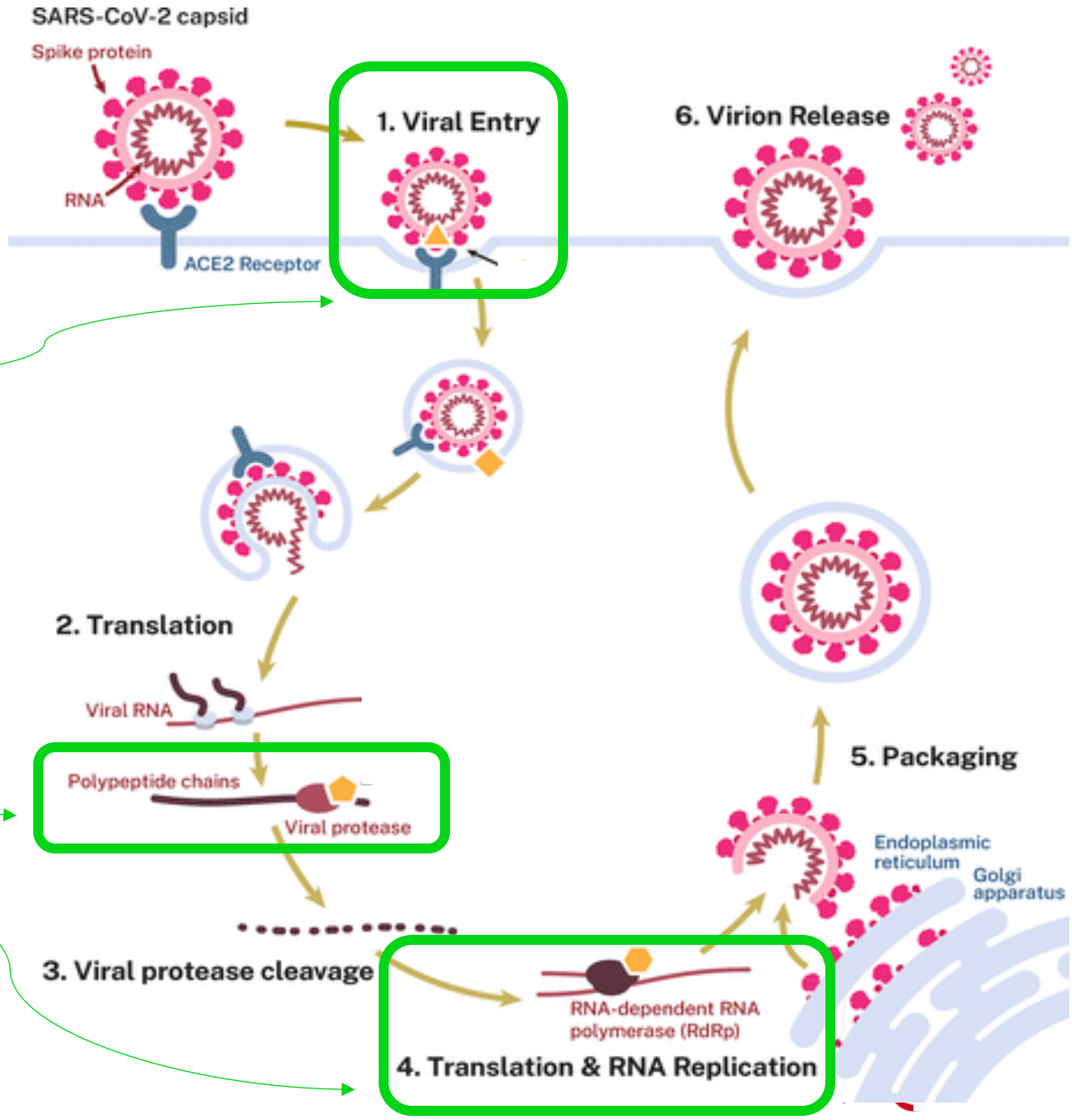
https://www.covid19treatmentguidelines.nih.gov/

Drug targets

Bebtelovimab
Tixagevimab-cilgavimab

Nirmatrelvir-ritonavir

Remdesivir
Molnupiravir



Eastman RT, et al. ACS Cent Sci 2020; 6(5):672-682

Nirmatrelvir-ritonavir

Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 12-years-old and ≥ 40 kg Symptom onset ≤5 days
Mechanism of action	Nirmatrelvir: inhibits main protease (Mpro) Ritonavir: inhibits CYP3A4-mediated metabolism of nirmatrelvir
Dosing	300mg-100mg (3 tabs) PO BID x **5 days**

Oral Nirmatrelvir-Ritonavir for High Risk, Non-hospitalized Adults with COVID-19 (EPIC-HR)

Population	Intervention	Outcome
• Non-hospitalized, mild to moderate disease • ≥ 1 risk factor for developing severe disease • Symptom onset within 5 days	• Nirmatrelvir-ritonavir (n=1039) • Placebo (n=1046)	• Primary: COVID-19 related hospitalization or death from any cause by day 28

Key Exclusion Criteria

- Prior COVID-19 infection or hospitalization for COVID-19
- Anticipated need for hospitalization within 48 hours of randomization
- **Received COVID-19 vaccine** or convalescent COVID-19 plasma
- Pregnancy or breastfeeding

Hammond J, et al. NEJM 2022

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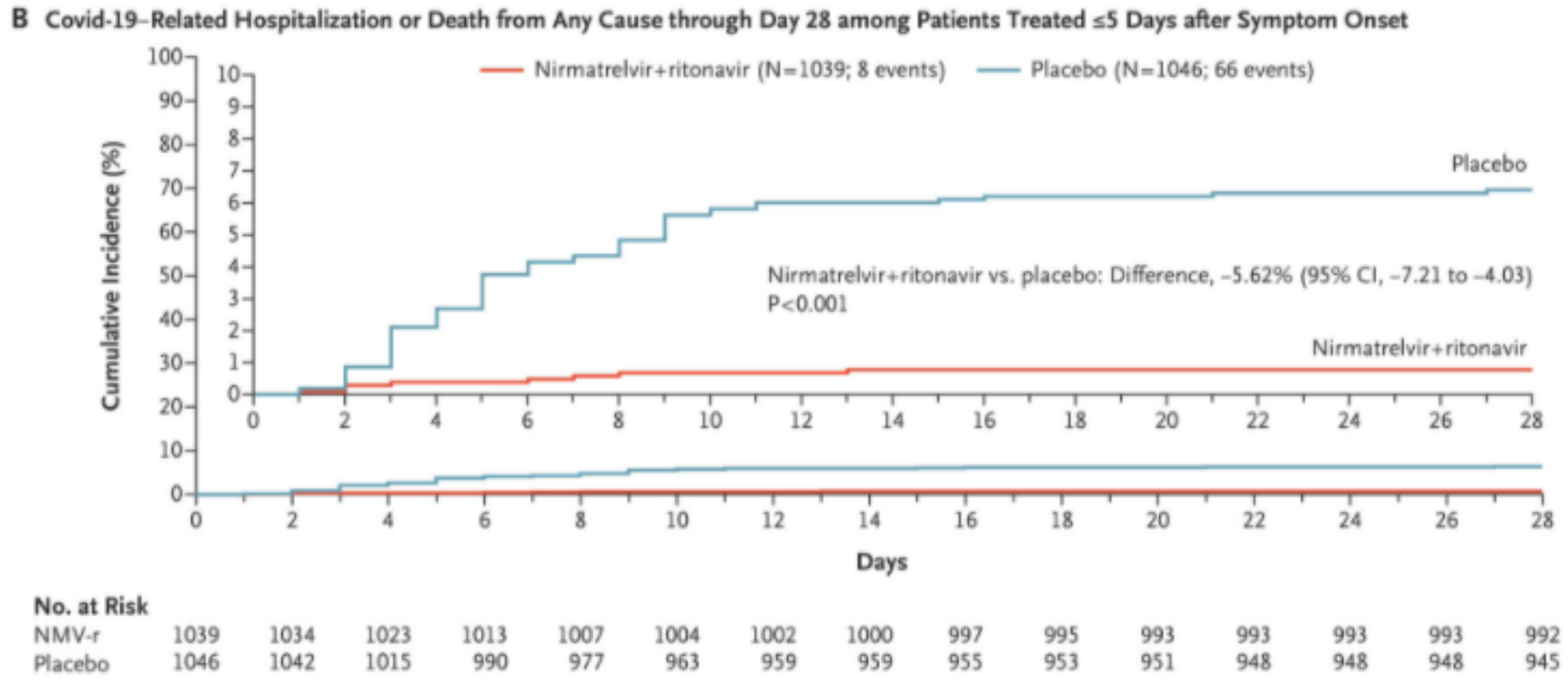
Oral Nirmatrelvir-Ritonavir for High Risk, Non-hospitalized Adults with COVID-19 (EPIC-HR)



- 88% lower risk of COVID-19 related hospitalizations or death
- Adverse effects of altered taste, diarrhea, hypertension, myalgia

Hammond J, et al. NEJM 2022

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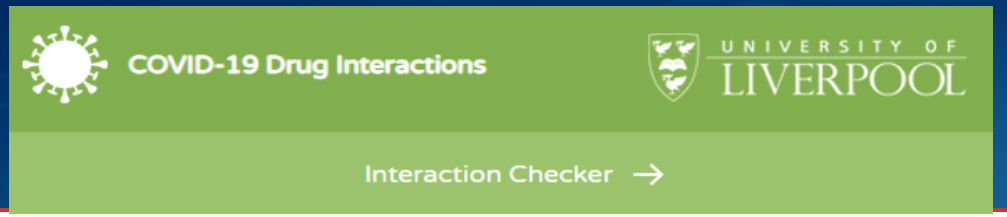
Check the medication list



- ✓ Use COVID-19 interaction checker to review medication list
- ✓ If drug interactions, evaluate whether medication can be held (i.e. statins) or dose reduced
- ✓ AVOID nirmatrelvir-ritonavir in patients who are taking :
  - ✓ Anti-rejection medications for transplant (tacrolimus, cyclosporine or sirolimus)
  - ✓ DOAC
- ✓ Oral contraceptives: additional method recommended while on nirmatrelvir-ritonavir

Drugs that are contraindicated

Cardiac	Ranolazine amiodarone, dronedarone, flecainide, propafenone, quinidine lovastatin, simvastatin
Anti-convulsants	Carbamazepine Phenobarbital Phenytoin Primidone
Antimicrobial	Rifampin Rifapentine
Herbal	St John's Wort
Misc and many more	Alfuzosin Colchicine Sildenafil (PAH) Ergotamine

Ritonavir-boosted nirmatrelvir. NIH COVID-19 treatment guidelines 2022
https://www.covid19-druginteractions.org/checker

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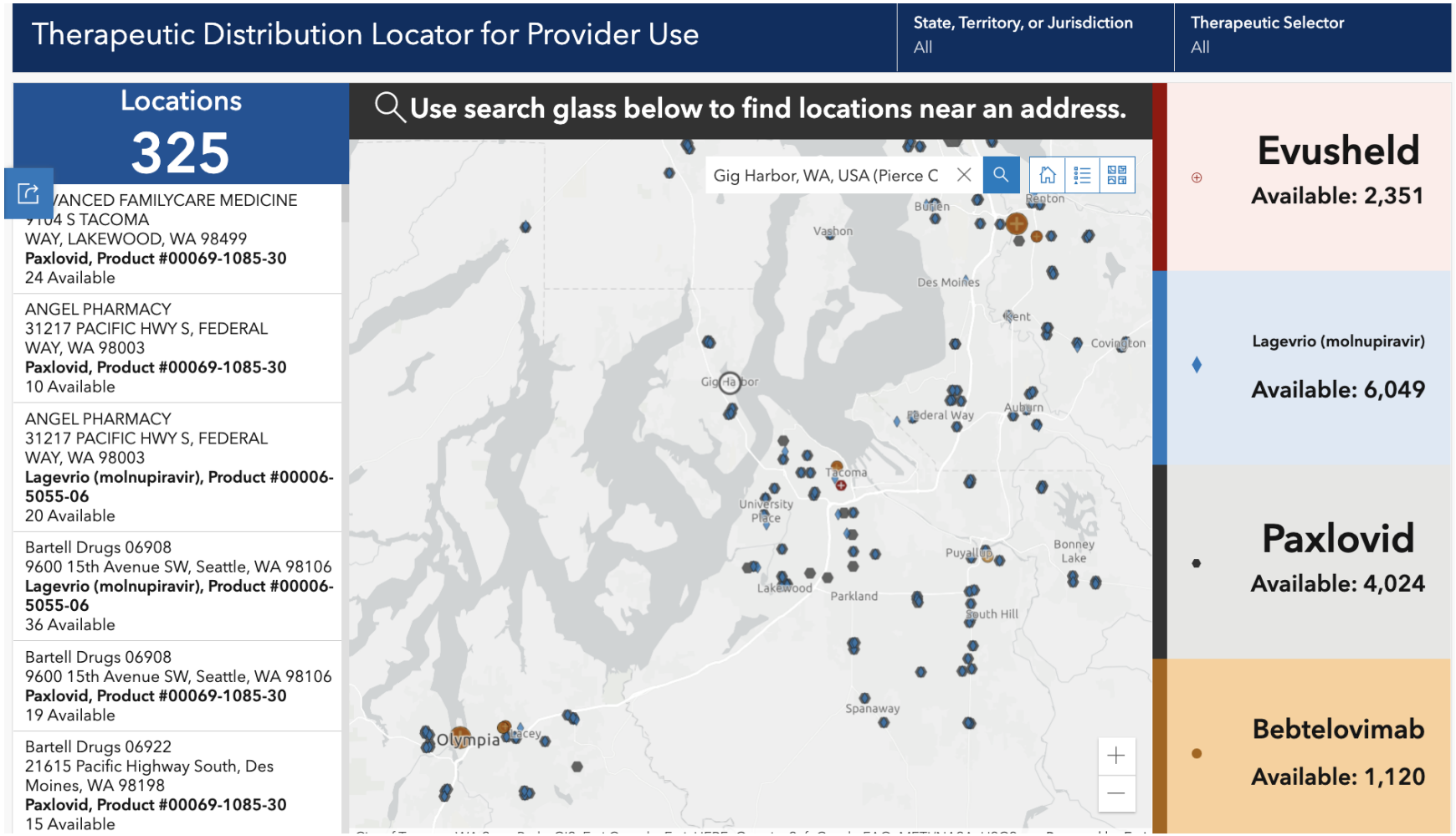
Where can I find nirmatrelvir-ritonavir?

Go to locator https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/



Bebtelovimab

Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 12-years-old and ≥ 40kg Symptom onset ≤7 days
Mechanism of action	Binds to spike protein of SARS-CoV-2
Dosing	175mg IV once
Not authorized	• hospitalized due to COVID-19 • require oxygen therapy and/or respiratory support due to COVID-19, • require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19

Bebtelovimab fact sheet. FDA 2022

BLAZE-4 Trial for Bebtelovimab

Phase 2 Data from the Randomized, Open-Label Portion

Outcome	BEB	BAM-ETE-BEB*
Hospitalization or death from any cause	3%	4%

*bamlanivimab + etesevimab + bebtelovimab combination therapy

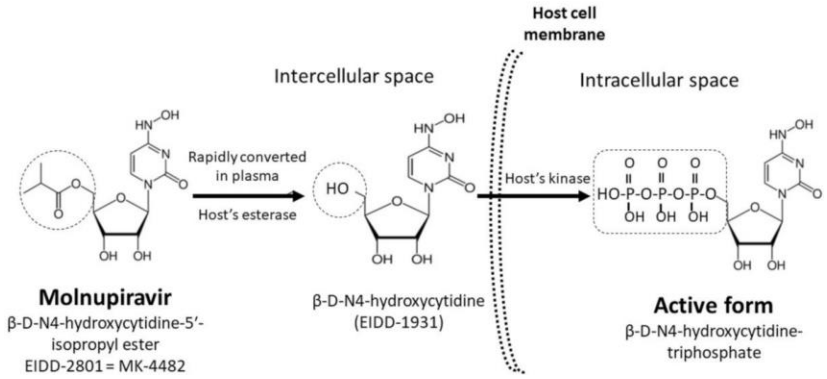
Conclusions

- Insufficient outcome data for patients at high risk for progression to severe disease
- Efficacy based on other therapeutics with similar mechanism and demonstrated benefit
- Potent activity against Omicron in vitro (BA.1 & BA.2 subvariants included)
- Adverse effects of nausea and vomiting

Bebtelovimab fact sheet. FDA 2022

Molnupiravir

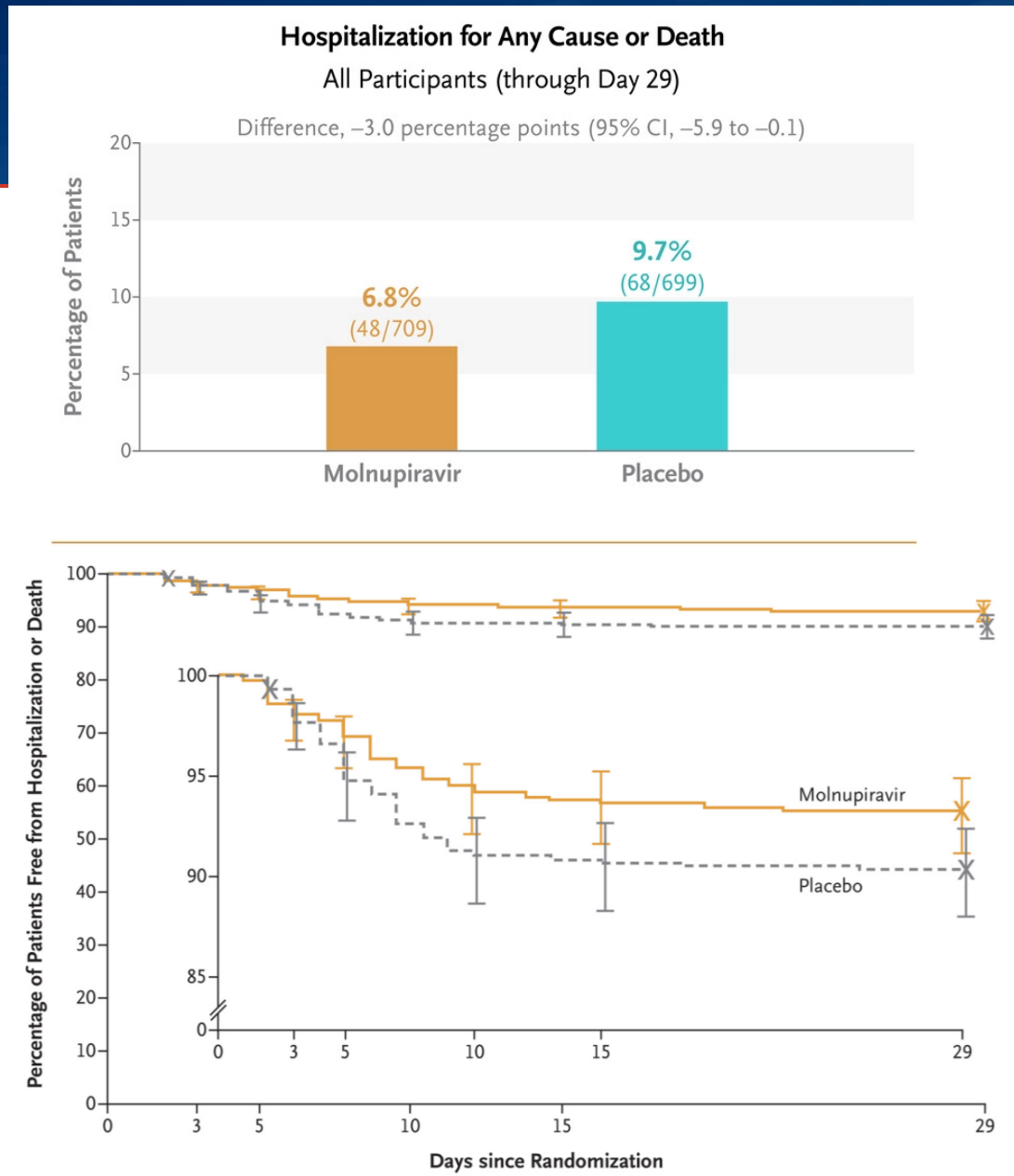
Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 18-years-old Symptom onset ≤5 days When alternative treatments are not accessible or clinically appropriate
Mechanism of action	Nucleoside analog prodrug of NHC
Dosing	800mg (4 caps) PO BID x5 days
Precaution	is not recommended during pregnancy



https://www.mdpi.com/2079-6382/10/11/1294/htm

Molnupiravir

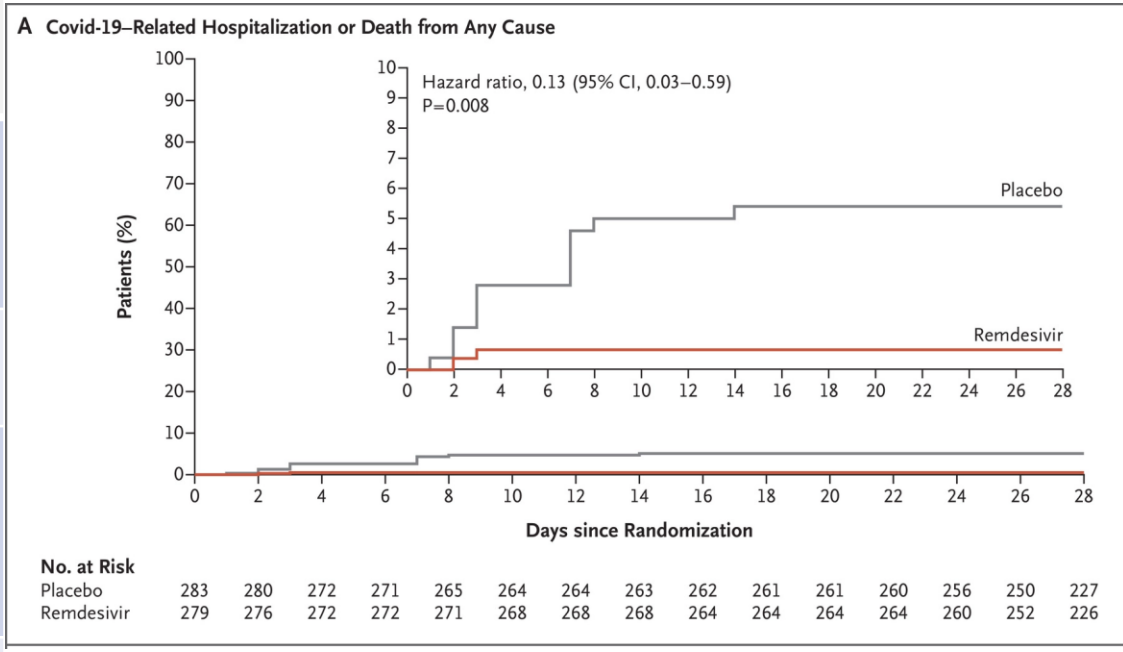
Population	Non-hospitalized, mild to moderate disease ≥ 1 risk factor for developing severe disease Symptom onset within 5 days
Intervention	Molnupiravir (n=716) Placebo (n=717)
Primary outcome	Primary: hospitalization or death by day 29



N Engl J Med 2022; 386:509-520
DOI: 10.1056/NEJMoa2116044

Remdesivir

Indication	Non-hospitalized with mild-moderate COVID-19 at high risk for progression to severe COVID-19 ≥ 12-years-old and ≥ 40kg Symptom onset ≤7 days
Mechanism of action	Direct acting nucleotide inhibitor of RNA-dependent polymerase
Dosing	200mg IV on day 1, then 100mg IV on day 2, 3
Population	Non-hospitalized, mild to moderate disease ≥ 1 risk factor for developing severe disease Symptom onset within 7 days
Outcome	Primary: COVID-19 related hospitalization or death Secondary: COVID-19 related medical visits or death



Gottlieb RL, et al. NEJM 2022; 386(4):305-315

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Pre-Exposure Prophylaxis

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Tixagevimab-cilgavimab

Indication	No known COVID-19 exposure and COVID-19 negative AND Immunocompromised or unable to receive vaccination ≥ 12-years-old and ≥ 40kg
Mechanism of action	Neutralizing mAbs targeting spike protein of SARS-CoV-2 at non-overlapping epitopes Passive immunity
Dosing	300mg-300mg IM x1 (previously 150-150mg) Two separate injections 3mL
Duration of protection	Unknown, depends on circulating variant*

FDA EUA Fact Sheet Updated June 2022 –
Repeat dosing every 6 months

Provider FACT sheet: https://www.fda.gov/media/154701/download

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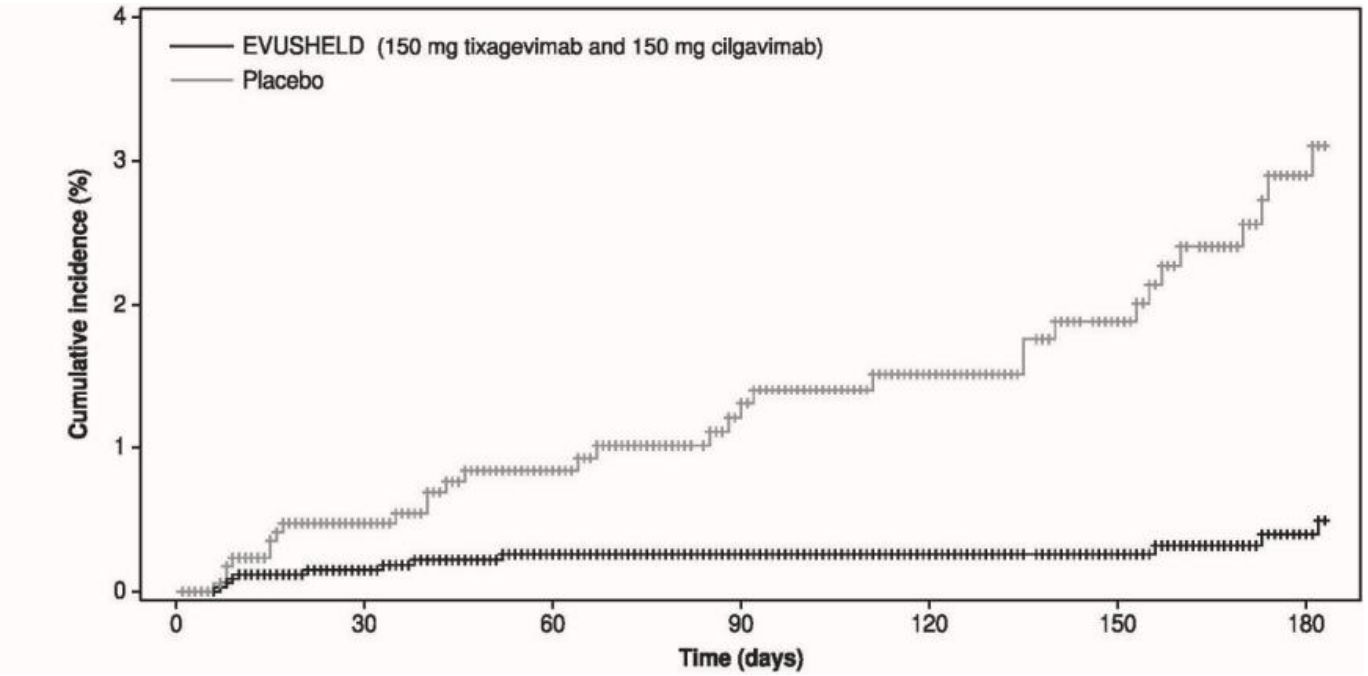
Tixagevimab-cilgavimab

	PROVENT Pre-exposure prophylaxis
Population	No known exposure and unvaccinated Would benefit from prevention ≥ 18 years old
Intervention	Placebo (n=1,731) tixagevimab-cilgavimab 150mg-150mg IM x1 (n=3,441)
Outcomes	Primary: incidence of COVID-19 positive cases by day 183 (6 month)
Results	77% reduction in symptomatic COVID-19 disease 69% reduction in COVID-19 disease or death from any cause

Cumulative Incidence of Symptomatic COVID-19



JAMA 2022;327(4):384-385
https://www.biospace.com/article/releases/evusheld-formerly-azd7442-long-acting-antibody-combination-authorized-for-emergency-use-in-the-us-for-pre-exposure-prophylaxis-prevention-of-covid-19/

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EUA Outpatient Therapies for COVID-19

Drug	Mechanism of Action	Population	Efficacy
Tixagevimab/cilgavimab	Long-acting monoclonal antibody (spike)	Pre-exposure prophylaxis • Immunocompromised, may not mount response OR • Unable to vaccinate	77% reduction in symptomatic COVID-19
Bebtelovimab	Monoclonal antibody (spike)	Early treatment*, high risk (NIH Tier 1 and Tier 2)	79% reduction in risk of hosp/death**
Nirmatrelvir/ritonavir	SARS-CoV-2 protease inhibitor	Early treatment*, high risk (NIH Tier 1- 4)	88% reduction in risk of hosp/death
Molnupiravir	Nucleoside analogue	Early Treatment*, high risk	30% reduction in risk of hosp/death
Remdesivir	Inhibits viral RNA polymerase	Early Treatment*, high risk (NIH Tier 1-3)	87% reduction in hospitalization

*within 7 days of symptom onset **based on other monoclonal therapies not bebtelovimab

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Questions?

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