Prescribing of Paxlovid for the treatment of COVID-19 in non-hospitalised patients

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Aim

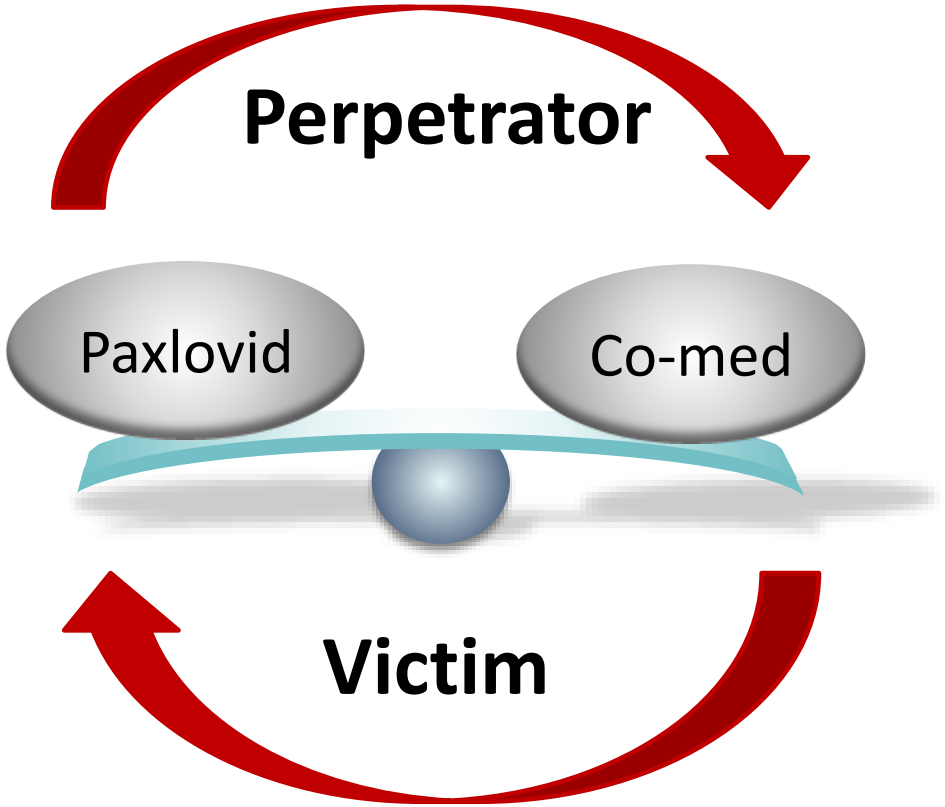
To provide prescribers and other healthcare professionals with an understanding of the new oral COVID-19 treatment, Paxlovid. This includes its effectiveness and place in treatment, and key information to support safe prescribing in practice.

Learning outcomes

At the end of the session, you should be able to:

- describe the clinical evidence and ongoing research related to Paxlovid (nirmatrelvir/ritonavir/) and other oral antivirals when treating COVID-19 in the community.
- explain how to prescribe and supply Paxlovid safely for the treatment of COVID-19 in appropriate patient groups.
- use appropriate resources to manage drug interactions and other contraindications for Paxlovid.

Understanding drug to drug interactions with Paxlovid (Nirmatrelvir/ritonavir)



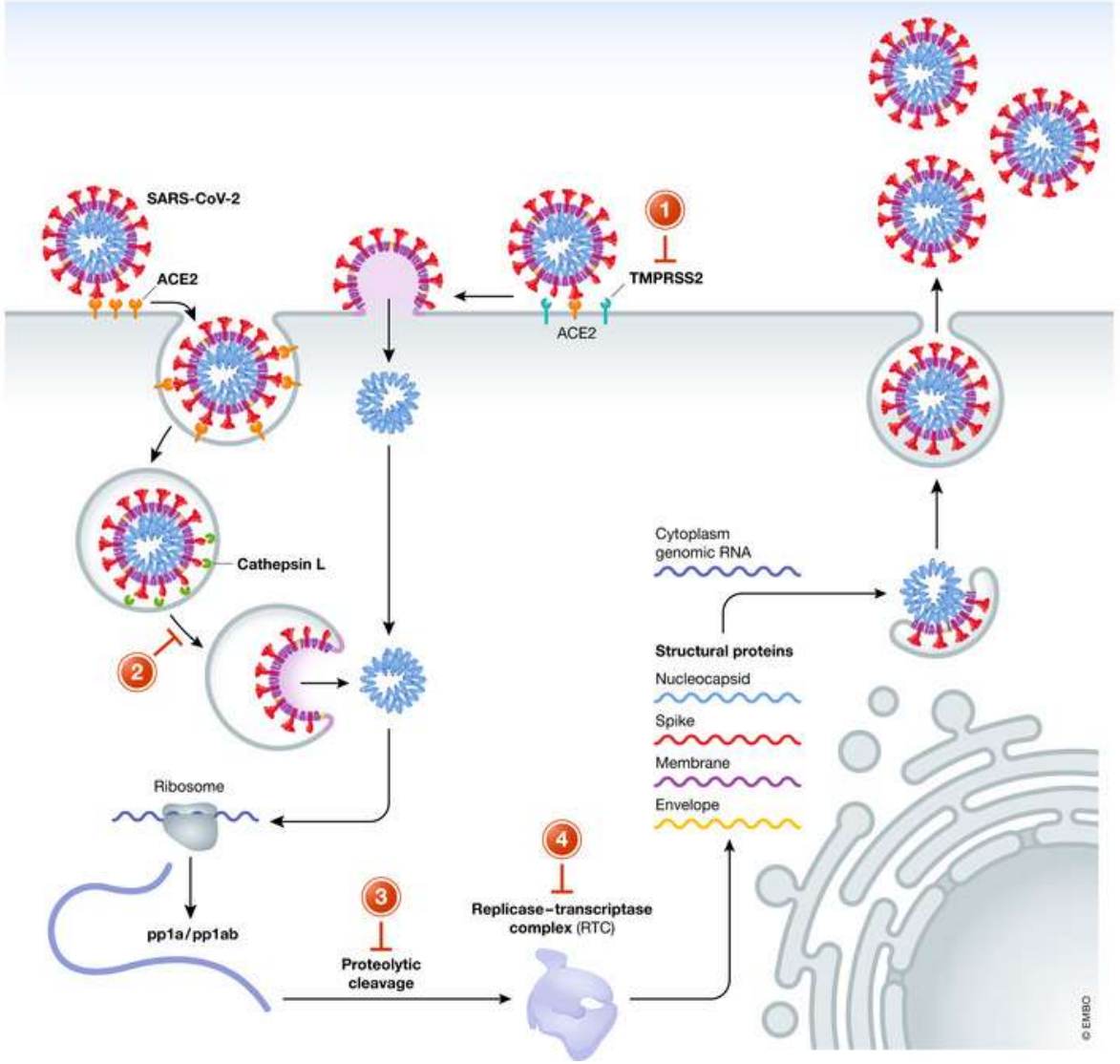
Overview

1. Paxlovid introduction
2. Understanding DDIs
3. Liverpool interaction checkers
4. Managing DDIs: Case Studies

What is PAXLOVID (Nirmatrelvir + Ritonavir)?

Nirmatrelvir + Ritonavir

- Nirmatrelvir is a SARS-CoV-2 protease inhibitor
- Ritonavir is a CYP3A inhibitor used as a pharmacokinetic enhancer (‘booster’) to increase nirmatrelvir plasma levels
  - Ritonavir alone has no activity against SARS-CoV-2
  - Ritonavir at higher doses was previously used as an HIV-1 protease inhibitor
  - It is now used only as a pharmacokinetic enhancer in HIV and HCV



A comparative analysis of remdesivir and other repurposed antivirals against SARS-CoV-2, EMBO Mol Med, Volume: 13, Issue: 1, First published: 04 October 2020, DOI: (10.15252/emmm.202013105).

Dosing and administration

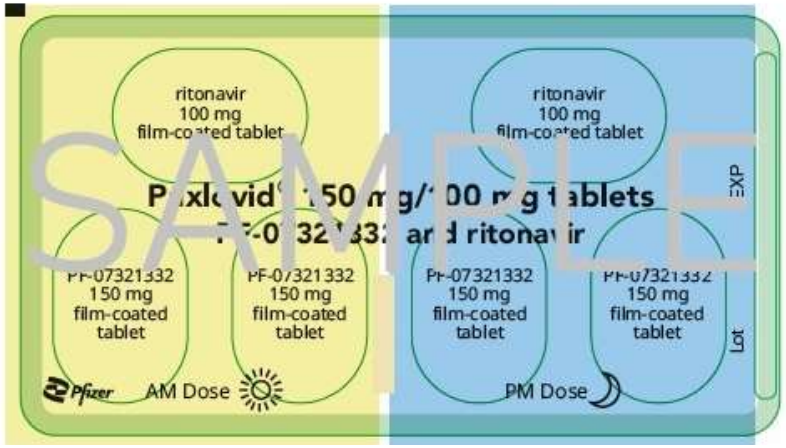
Dose: 2 x 150 mg tablets (300 mg) nirmatrelvir with one 100mg tablet ritonavir orally bid x 5 days

- No food requirement
- Swallow whole- no data on crushing
- Needs prescribed within 5 days of symptom onset
- Each box contains five blister packs, one for each day

Paediatric use

Paxlovid is not license in under 18's.

- Under 18's not included in EPIC-HR study
- Decades of experience of ritonavir from birth- may be reviewed?
- Paxlovid is authorized from age 12 years of age and older weighing at least 40 kg in US EUA so real world data may emerge soon



Dosing and administration

Renal Impairment

Mild renal impairment: No dose adjustment

***Moderate renal impairment:** Half dose: Nirmatrelvir 150mg (ONE tablet instead of TWO with full dose ritonavir)

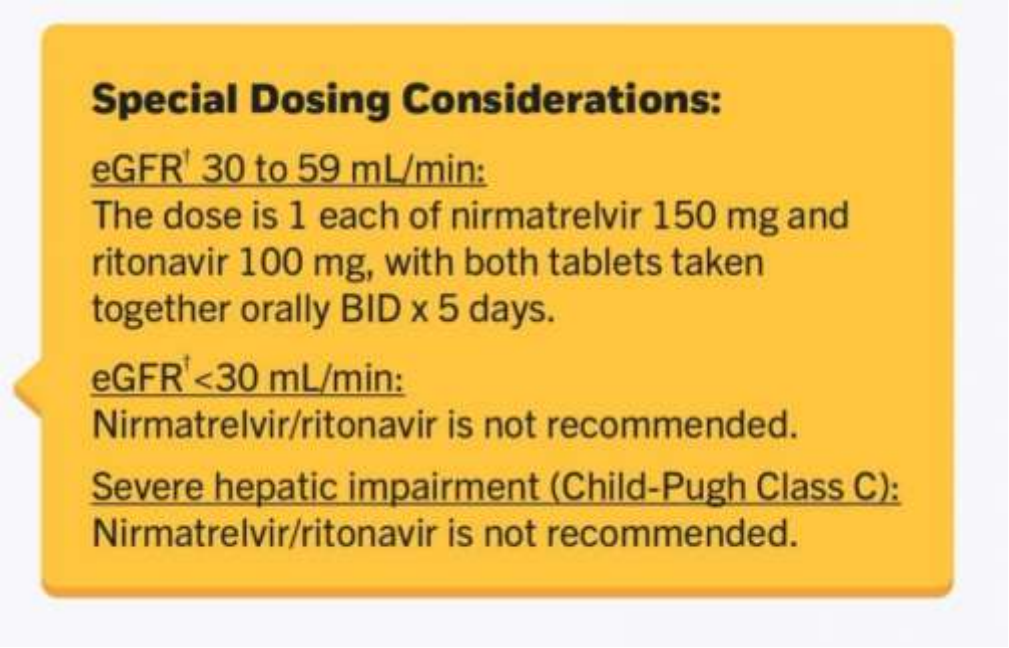
Severe renal impairment: Not recommended

Hepatic Impairment

Mild hepatic impairment (CPA): No dose adjustment

Moderate hepatic impairment (CPB): No dose adjustment

Severe hepatic impairment (CPC): Not recommended



* NB: UK commissioning document mentions avoiding in CKD 3-5, with specialist discussion at CK 3

Paxlovid SmPC,Accessed February 2022
https://covid19-sciencetable.ca/wp-content/uploads/2022/01/NirmatrelvirRitonavir-Paxlovid-What-Prescribers-and-Pharmacists-Need-to-Know_20220125.pdf

Dosing and administration

Pregnancy

- There are no data from the use of Paxlovid in pregnant women.
- Paxlovid is not recommended during pregnancy and in women of childbearing potential not using effective contraception.
- There was no PF-07321332-related effect on foetal morphology or embryo-foetal viability at any dose tested in rat or rabbit embryo-foetal developmental toxicity studies.
- Ritonavir use in HIV in pregnancy is common practice

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 so that they can be followed up. For more information go to http://www.uktis.org/".

Breastfeeding

- Breastfeeding should be discontinued during treatment and for 7 days after last dose

When to administer?

SPC: Paxlovid should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms.

NB. There is a provision in the commissioning policy, "*Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated*"

Data on Efficacy: EPIC-HR

- Phase 2/3 double-blind study in 2,246 non-hospitalized, symptomatic adults with a laboratory-confirmed SARS-CoV-2 infection who were randomized 1:1 to receive Paxlovid or placebo for 5 days.

- Population:
  - Enrolled within 5 days of symptom onset
  - ≥1 risk factor for progression to severe disease
  - No prior COVID-19 vaccine receipt or prior COVID-19 infection
  - Standard of care treatment allowed, but the primary analysis population was limited to subjects who did not receive COVID-19 monoclonal antibodies (mAbs

*More information about the study EPIC-HR:
https://clinicaltrials.gov/ct2/show/NCT04960202

Data on Efficacy: EPIC-HR

Efficacy Results in Non-Hospitalized Adults with COVID-19 Dosed within 5 Days of Symptom Onset who Did Not Receive COVID-19 mAb Treatment at Baseline

	PAXLOVID (N=1,039)	PLACEBO (N=1,046)
Primary endpoint: COVID-19 related hospitalization or death from any cause through Day 28 n(%)	8 (.08%)	66 (6.3%)
Reduction relative to placebo for primary endpoint a [95%, CI], %	-5.62 (-7.21,-4.03)	
All-cause mortality through Day 28, %	0	12 (1.1%)

a The estimated cumulative proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through Day 28 were censored at the time of study discontinuation.

- 88% (95% CI: 75%, 94%) relative risk reduction for the primary endpoint (proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28)
- Treatment effect was generally consistent across subgroups, including baseline serology status.

Other COVID-19 treatment efficacy data

COVID treatment	Relative risk reduction compared to placebo at day 28
Paxlovid[1]	88%
Sotrovimab[2]	79%
Remdesivir[3]	86%
Molnupiravir[4]	30%

1. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the Neutralizing SARS-CoV-“ Antibody Sotrovimab in Preventing Progression of COVID-19: A Randomized Clinical Trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.11.03.21265533v1
3. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients [published online ahead of print, 2021 Dec 22]. N Engl J Med. 2021;NEJMoa2116846. doi:10.1056/NEJMoa2116846
4. Bernal AJ, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Non-hopitalised Patients [published online ahead of print, 2021 Dec 16]. N Engl J Med. 2021; 10.1056/NEJMoa2116044. doi: 10.1056/NEJMoa2116044

Drug Interactions

- Nirmatrelvir is a CYP3A4/P-gp substrate that undergoes renal excretion
- Ritonavir is a potent **inhibitor** of CYP3A4, CYP2D6 and P-gp inhibitor and is also metabolized by CYP3A4.
- Ritonavir is an **inducer** of CYP1A2, CYP2C8, CYP2C9 and CYP2C19

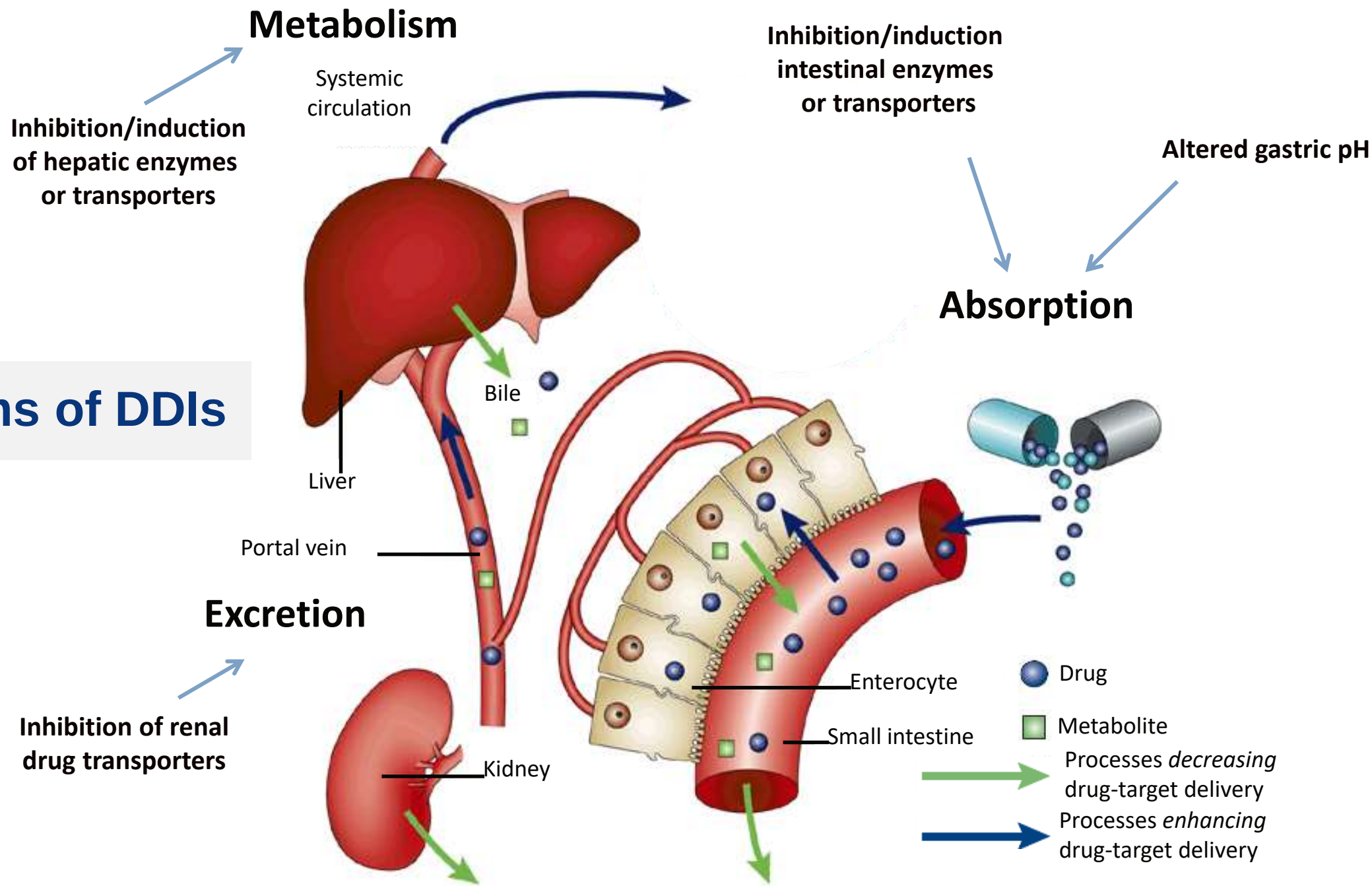
Inhibition interactions by ritonavir can occur in 24-48 hours: **SIGNIFICANT** FOR PAXLOVID

Induction interactions by ritonavir take up to 14 days to occur: **NOT SIGNIFICANT** FOR PAXLOVID

Other drugs affecting Paxlovid:

- Induction interactions *caused by inducing co-medications* such as carbamazepine are contraindicated as will significantly reduce concentrations and efficacy of Paxlovid. Stopping the inducing drug will not avoid these interactions.

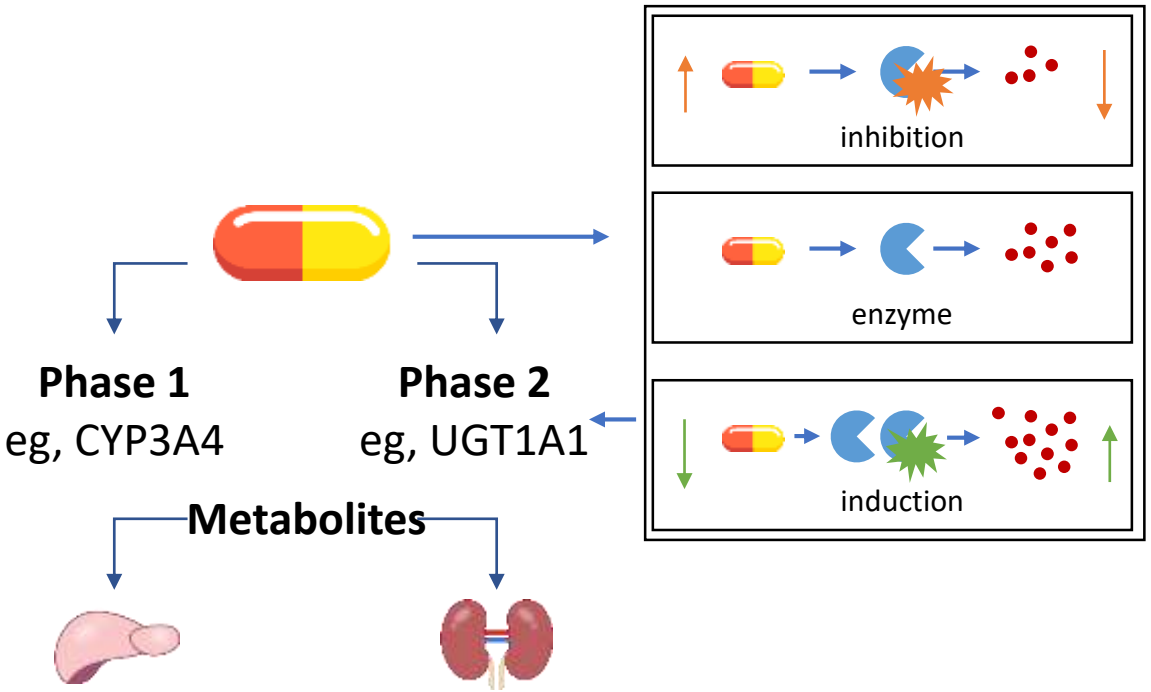
Mechanisms of DDIs

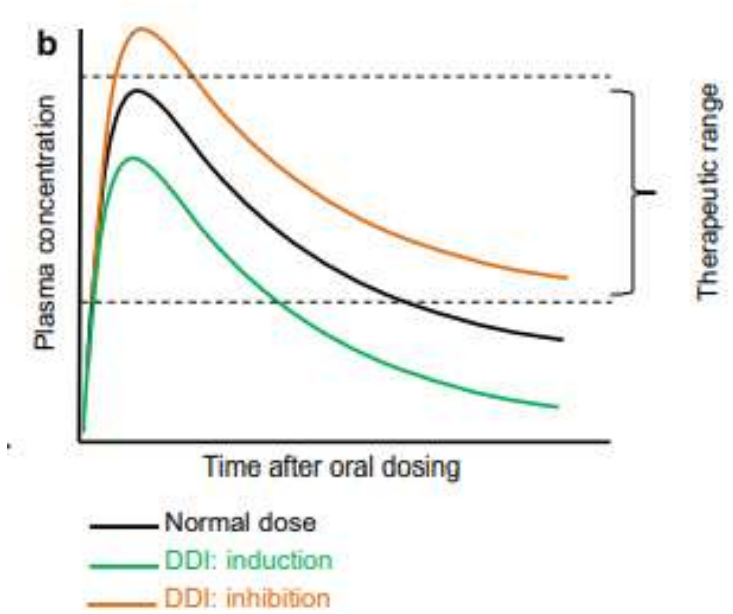


Reference: Roden DM & George AL Jr. *Nat Rev Drug Discov* 2002; **1**:37–44; Personal communication: Prof. David Back.

Examples of Enzyme Induction and Inhibition

Potential effect on the drug exposure in plasma?





Inhibitors
Ritonavir/Cobicstat
Azoles
Macrolides
Ciprofloxacin

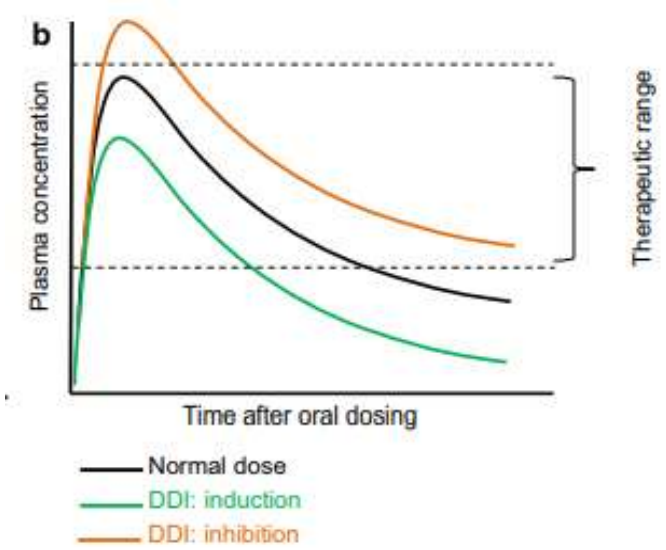
Inducers
Rifampicin
Carbamazepine
St John's wort
Efavirenz
Modafinil

UGT=UDP glucuronosyltransferase.

Modified by D Back from Smolders EJ. et al. *Clin Pharmacokinet.* 2019;58(10):1237-1263.

What is a Clinically Significant Interaction?

In drug development phase drug interaction (DDI) studies concentrate on PK (ie plasma concentration changes).



The clinical need is to assess the risk of harm from a DDI in patients who often have complex comorbidities (including renal or hepatic impairment)

- In liver disease (cirrhosis) maybe altered enzyme/ transporter expression, liver blood flow, protein binding.

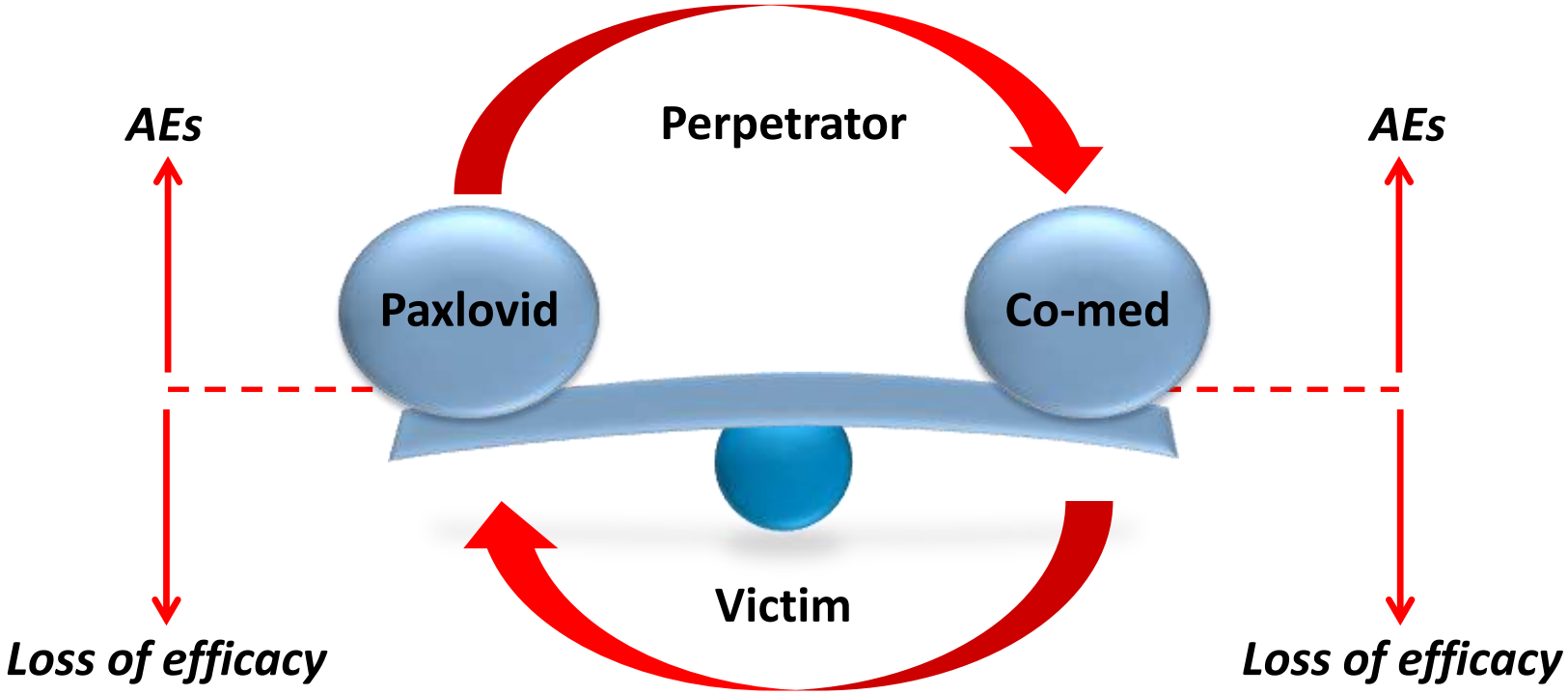
Period of tx exposure

- **HIV:** Lifelong
- **HCV:** 8-12 weeks
- **Covid-19**: 5 days for paxlovid

Risk–benefit assessment

- Can DDIs be avoided?
- Can a drug be stopped?
- Is additional monitoring required?

Drug–Drug Interactions (DDIs)



Need to understand:

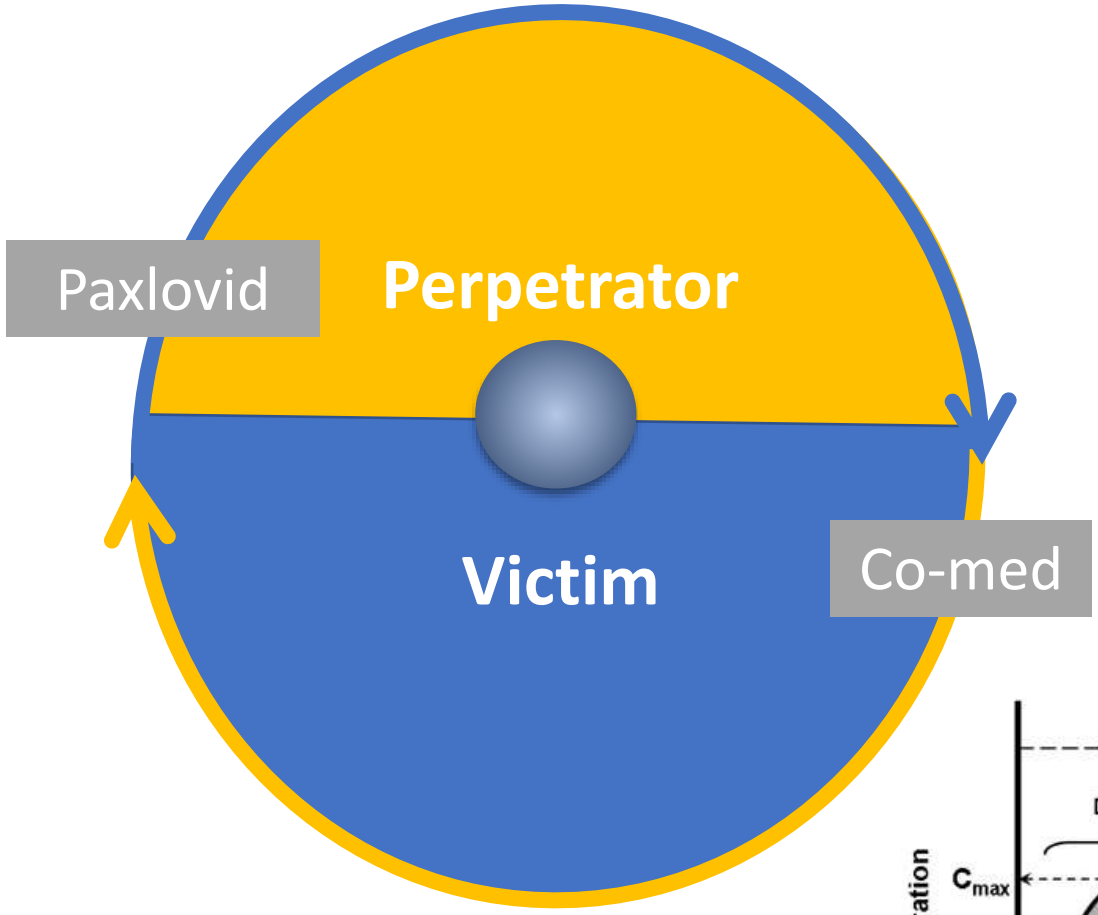
- The disposition or handling of each drug
- The therapeutic window of each drug

AEs = adverse events.

The Problem of DDIs: Predominantly Pharmacokinetic

‡

Toxicity
↑
Therapeutic Window
↓
Lack of Efficacy



Toxicity
↑
Therapeutic Window
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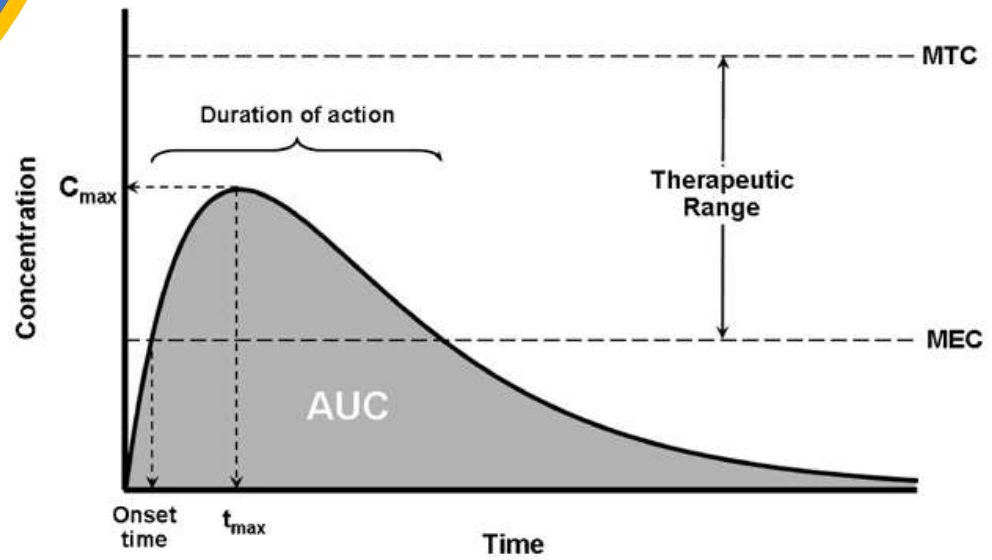
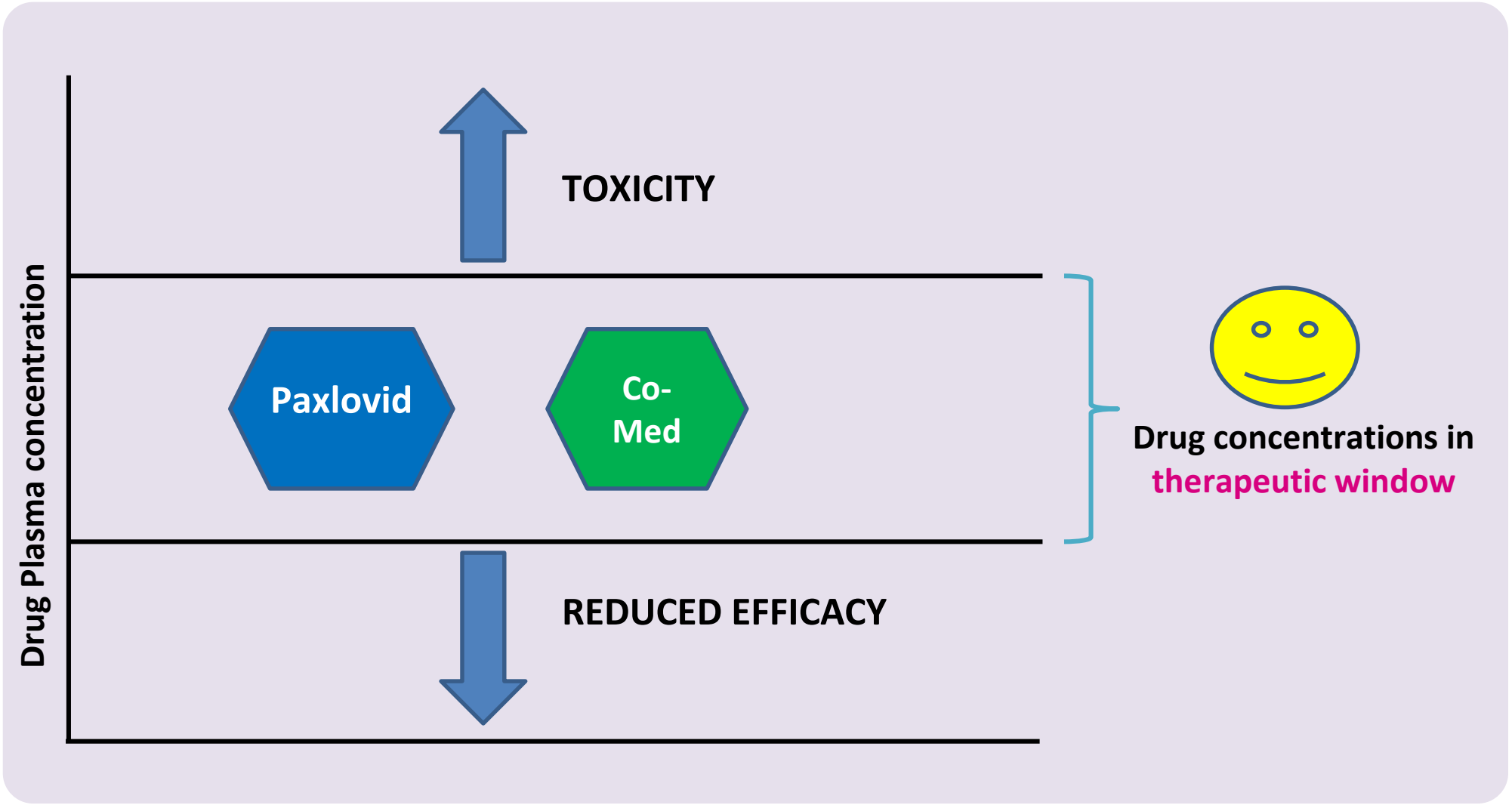
Lack of Efficacy



AUC=area under the curve; C_{max}=maximum drug concentration; MEC=minimum effective concentration; MTC=minimum toxic concentration; T_{max}=time to reach maximum concentration.

Mehrota N, et al. *Int J Impot Res*. 2007;19(3):253-264.

Therapeutic Window



Taking a drug history

Check ALL medicines:

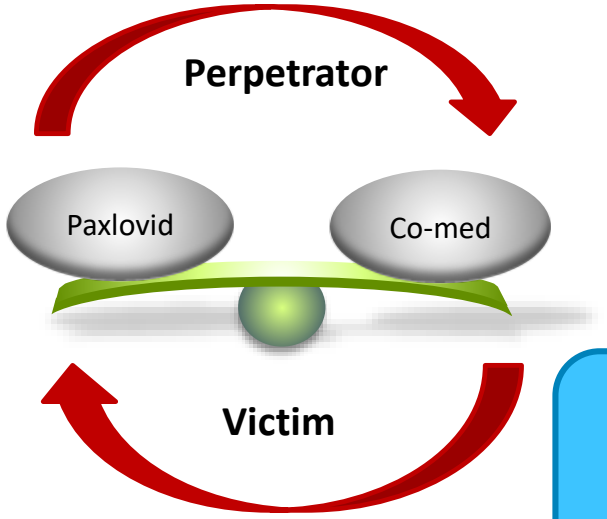
- OTC
- Recreational drugs
- Hospital supplied such as:
  - SACT
  - OST
  - HCV/HIV/HBV treatment
  - Contraception
  - Steroid Injections
  - Depot antipsychotics

Multimorbidity

Polypharmacy *(Inc non-prescription drugs/supplements etc)*

'Polydoctory'

DDIs



Reduced efficacy of agent?

Reduced efficacy of co-medication?*

Adverse effect?

Age-related Pharmacokinetic & Pharmacodynamic change

*Induction interactions take ~14 days, not an issue in 5 day course

Liverpool Websites- Some history

- Accessed from **188 countries** across the world
- In the past 3 years **around 8.5M** DDIs downloaded;
- Recommended tool for **over 30 national or international HIV/HCV guidelines** including WHO, European AIDS Clinical Society, British HIV Association, European Associations of Society of Liver (EASL), American Liver Society (AASLD)
- Database linkage for **electronic prescribing** in Uganda and Australia
- Translations into **Japanese** in 2017, Spanish version launched 2019

www.hep-druginteractions.org

Includes 26 drugs or regimens for treating HCV, HBV, hepatocellular carcinoma (HCC), primary biliary cholangitis (PBC) and 836 co-meds.

Each month ~15,000 users visit the site

Between August 2020 and July 2021, ~1.3 million interaction searches were made.

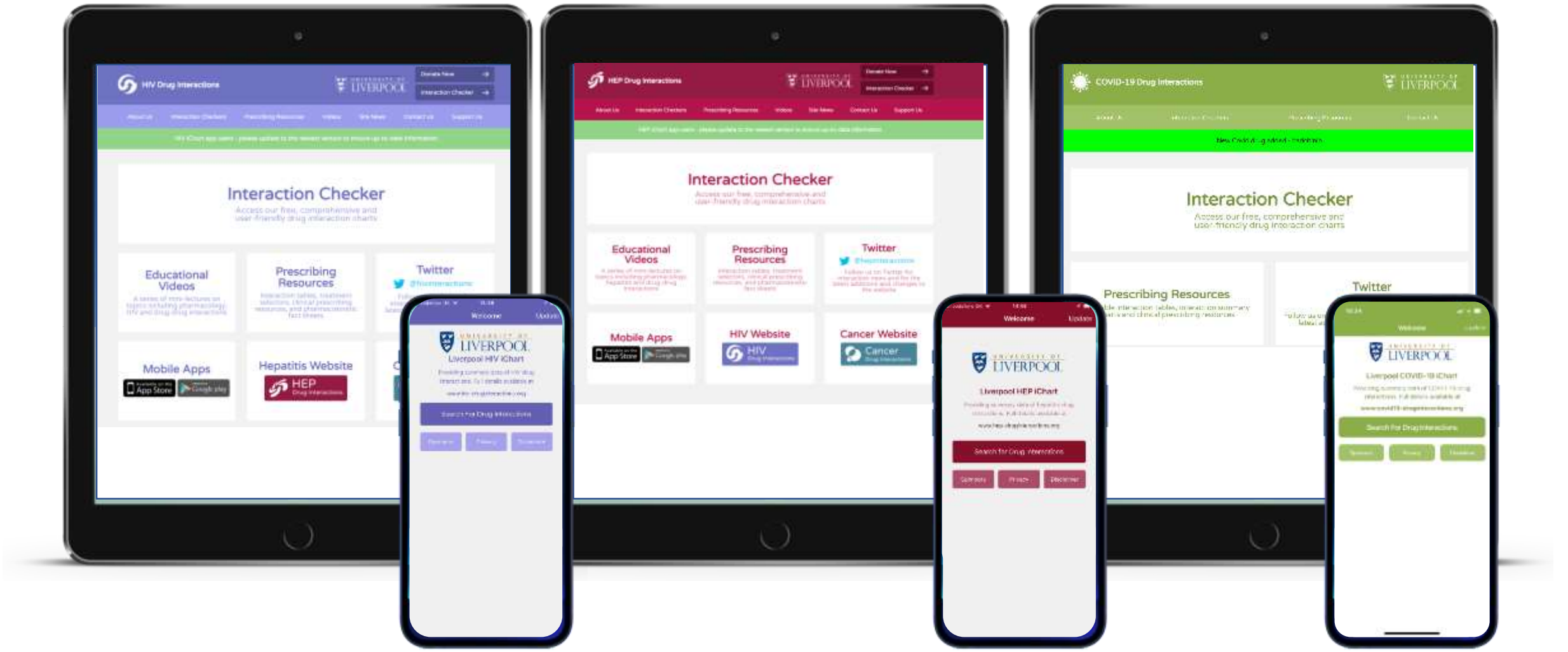
HIV Drug Interactions

Includes 44 drugs or regimens for treating or prevention of HIV and 814 co-meds.

Each month ~31,000 users visit the site

Between August 2020 and July 2021, ~2.9 million interaction searches were made.

DDI Resources – Apps and desktop versions



www.hiv-druginteractions.org; www.hep-druginteractions.org; www.covid19-druginteractions.org

https://www.covid19-druginteractions.org

COVID-19 Drug Interactions

UNIVERSITY OF LIVERPOOL

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Interactions with **PAXLOVID** (nirmatrelvir/ritonavir) and **EVUSHELD** (tixagevimab/cilgavimab) now available

Interaction Checker

Access our free, comprehensive and user-friendly drug interaction charts

Discover Our COVID-19 iChart Mobile App

COVID-19 iChart gives easy access to our drug interaction information on mobile devices.
Click the links below to get the app for your iPhone or Android device.

Download on the App Store

GET IT ON Google Play

How we make our evaluations

The scale in use of experimental therapies for COVID-19 is unprecedented. Accepting that evidence of benefit remains to be established for these agents, we have sought to make our drug-drug interaction (DDI) recommendations evidence-based, pragmatic and clinically useful. This has meant that, in addition to our usual criteria (Seden *et al*, 2017), we have also taken into account:

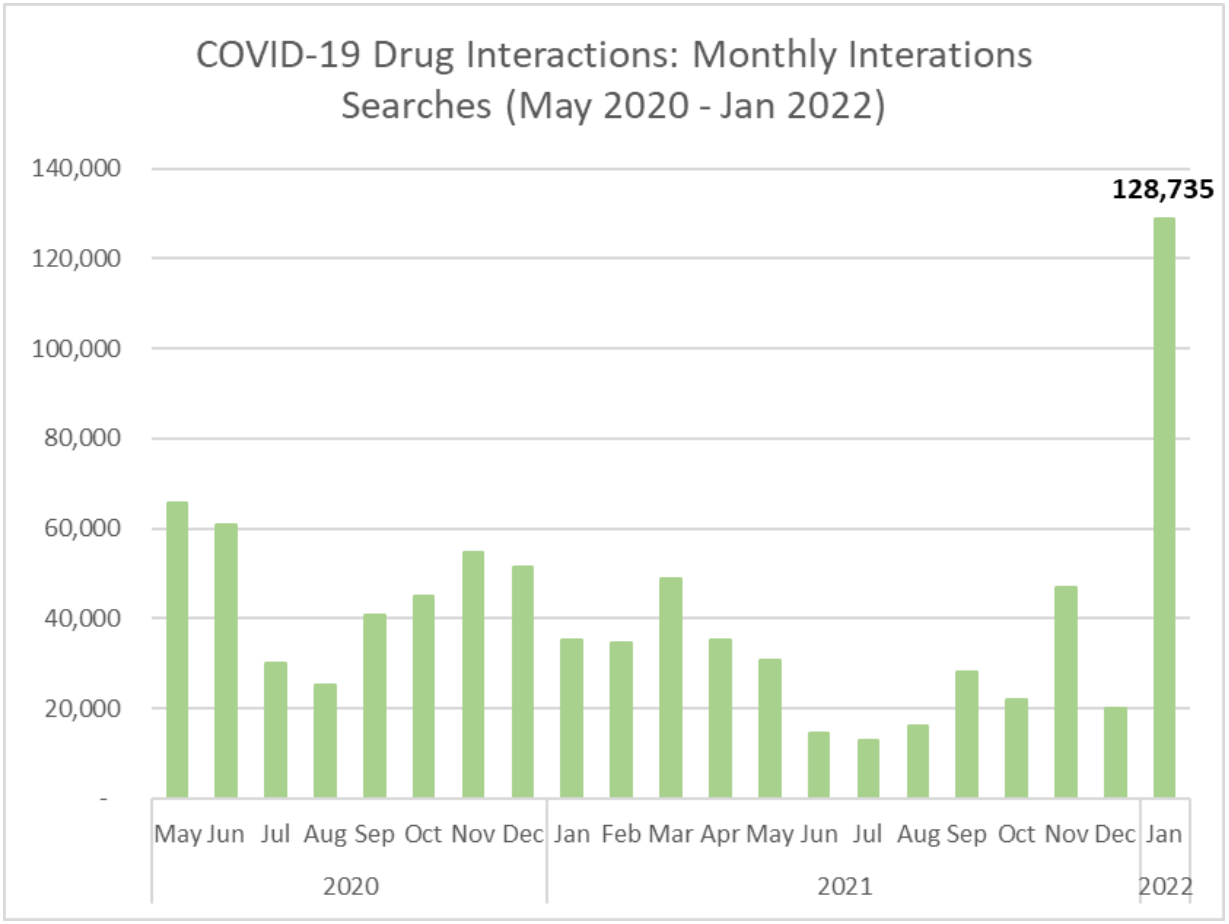
- the likely critical condition of any patient requiring these therapies
- the relatively short duration of co-administration
- the incremental risks to health workers from additional monitoring
- the available, safer alternatives
- the option of pausing the co-medication whilst COVID therapy is administered

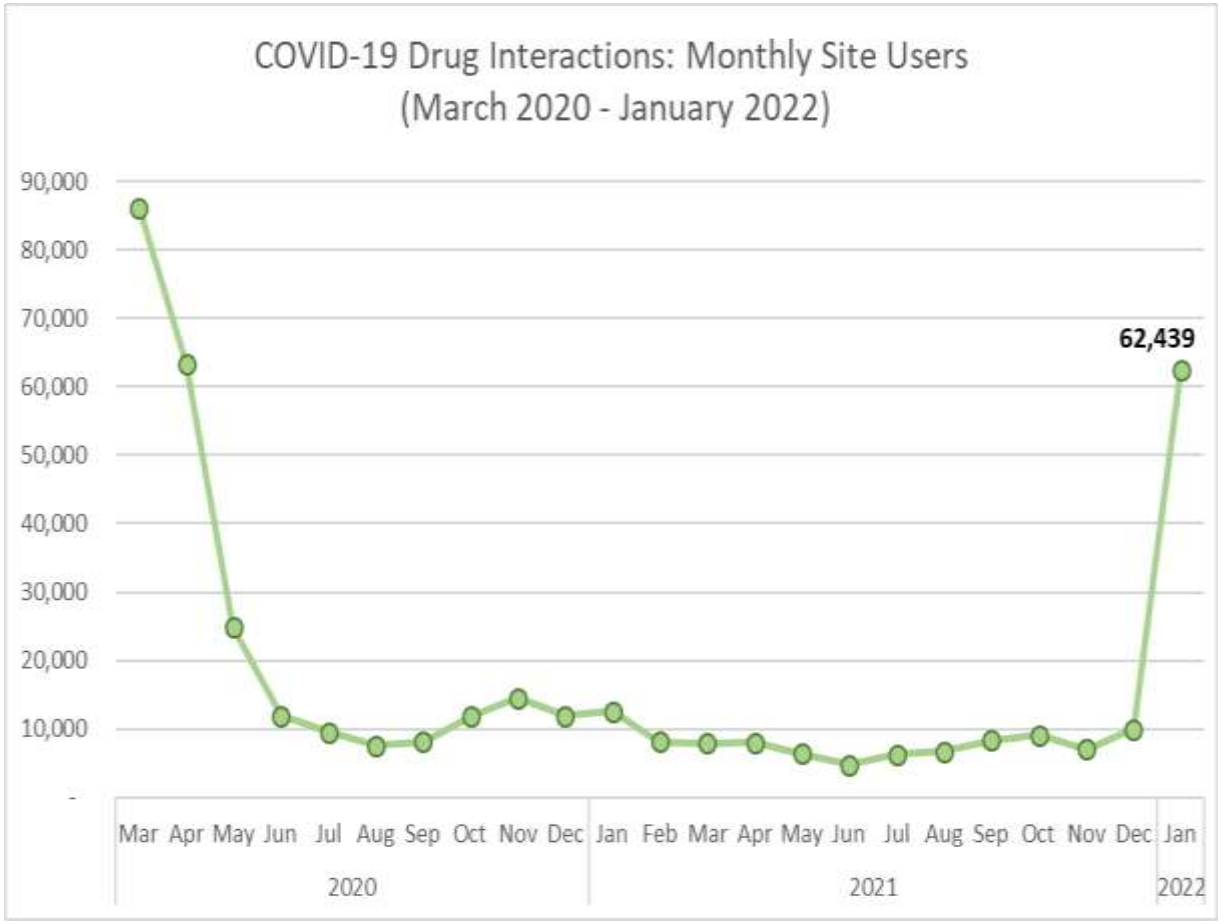
We always strive to make recommendations based on knowledge and evidence, and to be transparent and accountable. Some COVID therapies have few published data, so we have resorted to using what we can get hold of. Therefore, the quality of evidence for all unpublished data should be regarded as very low.

In the sections below, we have summarised our understanding of the pharmacology of COVID-19 therapies (licensed and under clinical investigation) and the basis on which our DDI evaluations have been made. In addition, the CredibleMeds.org website was used to identify drugs with known, possible or conditional risks of QT prolongation and/or TdP. The risk may be increased when combining drugs as a result of pharmacodynamic (additive effect) and/or pharmacokinetic (increase in exposure) DDIs.

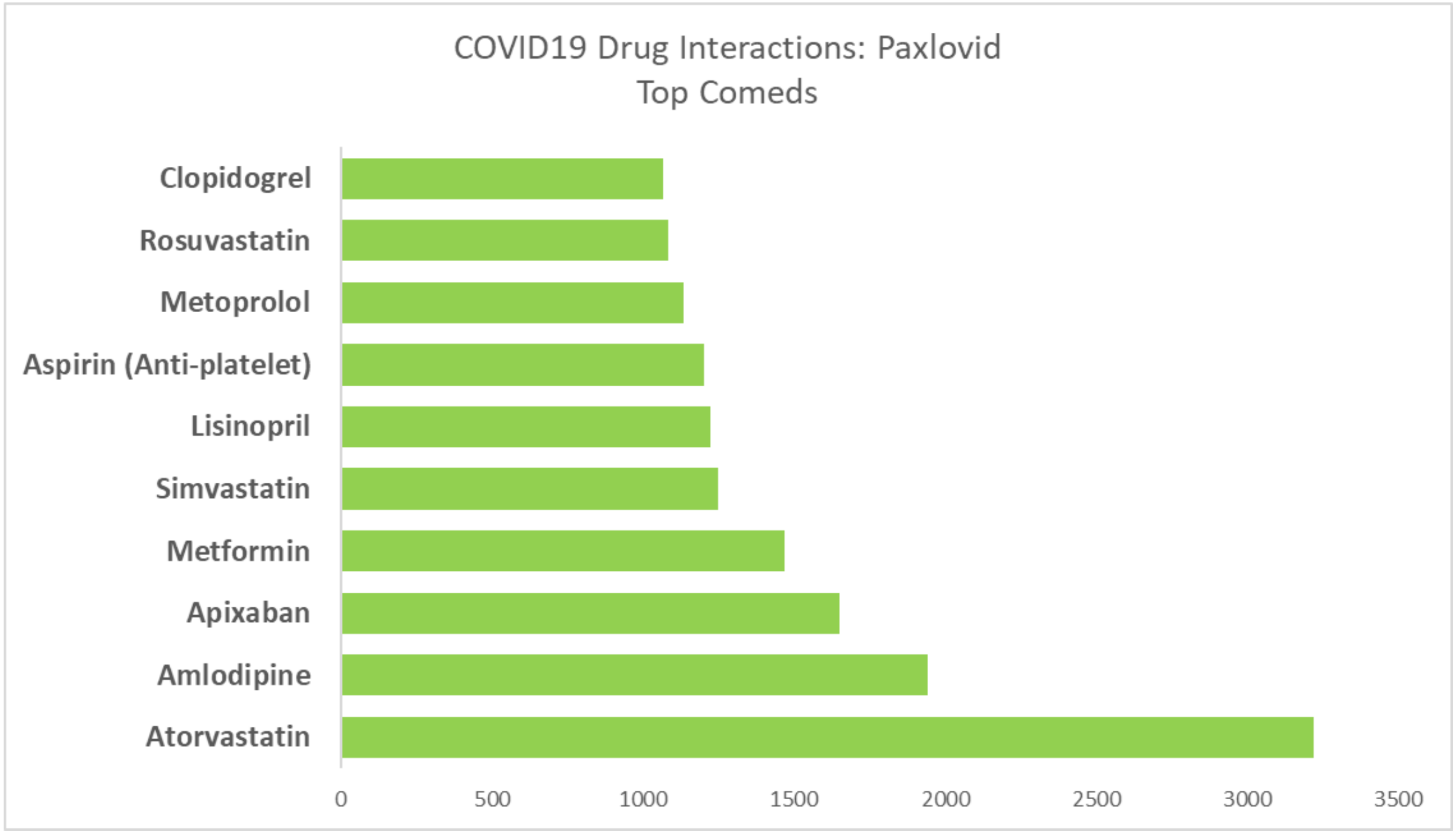
The decision to give or withhold drugs is always the responsibility of the prescriber. A pragmatic use of our DDI recommendations is to regard **Green** and **Yellow** flags on the interaction checker as an indication that no clinically significant DDIs exist, while **Red** flags indicate significant cause for concern. An **Amber** flag does not preclude co-administration (since DDIs are usually manageable), but rather indicates the need to consider risks and benefits in that individual patient for whom treatment is considered.

Paxlovid Interactions





Users from over 180 countries & territories


COVID19 Drug Interactions: Paxlovid
Top Comeds
Clopidogrel
Rosuvastatin
Metoprolol
Aspirin (Anti-platelet)
Lisinopril
Simvastatin
Metformin
Apixaban
Amlodipine
Atorvastatin
0
500
1000
1500
2000
2500
3000
3500

Managing drug interactions

Drugs contraindicated in the license due to CYP3A4 inhibition by ritonavir

- Do not co-administer

BUT

- Can the drug be safely stopped?

Do Not Coadminister

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Simvastatin

Quality of Evidence: Very Low

Summary:

Coadministration of simvastatin and potent CYP3A4 inhibitors, such as ritonavir, is contraindicated due to the high risk of presenting serious reactions such as risk of myopathy including rhabdomyolysis. It is highly advised to stop simvastatin during nirmatrelvir/ritonavir treatment. The pragmatic approach to stop temporarily simvastatin (or any other statins) is acceptable considering that it will not negatively affect the therapeutic effect but can minimize the risk for adverse events related to a drug interaction. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, simvastatin treatment will have to be resumed 3 days after the last dose of nirmatrelvir/ritonavir.

Description:

Coadministration is contraindicated due to increased plasma concentrations of simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis. HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated.

Paxlovid Summary of Product Characteristics, Pfizer Ltd, January 2022.

Do Not Coadminister

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Amiodarone

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied and is contraindicated. Amiodarone is metabolised by CYP3A4 and concentrations may be increased due to inhibition of CYP3A4 by nirmatrelvir/ritonavir thereby increasing the risk of arrhythmias or other serious adverse reactions. Note, amiodarone has a long elimination half-life and the risk of drug-drug interactions may not be overcome even by stopping amiodarone administration. Consider an alternative COVID-19 treatment.

Description:

Coadministration is contraindicated. Potentially increased plasma concentrations of amiodarone may result in arrhythmias or other serious adverse effects. Ritonavir coadministration is likely to result in increased plasma concentrations of amiodarone.

Paxlovid Summary of Product Characteristics, Pfizer Ltd, January 2022.

Co-administration may increase amiodarone concentrations. Co-administration contraindicated due to potential for cardiac arrhythmias.

Paxlovid FDA Emergency Use Authorisation, Pfizer Inc, December 2021.

Guidance for when to restart paused comedications or re-adjust dosage of comedications

Background

- Paxlovid (nirmatrelvir/ritonavir) has a high potential to cause clinically significant drug-drug interactions due to boosting with ritonavir and notably its potent inhibition of CYP3A4.
- Clinically significant drug-drug interactions can occur even though the duration of Paxlovid treatment is short as the onset of inhibition is rapid after starting ritonavir - maximal inhibition of CYP3A4 is reached ~48 hours after initiating ritonavir [1].
- Management of drug-drug interactions with Paxlovid may be complex and full details should be obtained from www.covid19-druginteractions.org. Management may include **pausing the administration** of comedications or **adjusting the dosage** of comedications.
- Importantly, CYP3A4 inhibition by ritonavir lasts several days after ritonavir is discontinued as it irreversibly inhibits CYP3A4 leading to loss of enzyme [1].
- Modelling data have shown that CYP3A4 inhibition significantly resolves 3 days after stopping ritonavir in most young and elderly individuals [2]. However, the inter-individual variability should be highlighted as a few individuals may have a slower disappearance of CYP3A4 inhibition [1,2]. In addition, the effect of ritonavir on drug concentrations may take longer to disappear for drugs characterized by a longer elimination half-life. Nevertheless, the timeline for pausing drugs should also factor in the critical indication of some drugs and the declining inhibitory effect.

"Three-Day" Recommendation

Based on the above considerations, we recommend:

Paused comedications can be restarted 3 days after the last dose of Paxlovid.

Adjusted comedications can be re-adjusted to pre-Paxlovid dosage 3 days after the last dose of Paxlovid.

No interaction expected

Potential weak interaction: no action required

Potential interaction: Dose adjustment or additional monitoring may be required

contraindicated / should not be co-administered

This is the problem- but made easier with short course !

No interaction expected

Potential weak interaction: no action required

Potential interaction: Dose adjustment or additional monitoring may be required

contraindicated / should not be co-administered

This is the problem- but made easier with short course !

Managing drug interactions

Drugs with a caution in license or based on PK where an interaction may occur.

Consider:

- The advice given and magnitude of interaction
- Is it occurring in an 18 yr old on one other medication or 75 year old with renal impairment and 12 other drugs?
- Can the patient be counselled to manage any additional side effects?
- Can they stop the drug? Yes in many cases

Managing drug interactions – keeping it simple

- Is the drug an absolute contraindication where stopping the medication will not circumvent the affect?

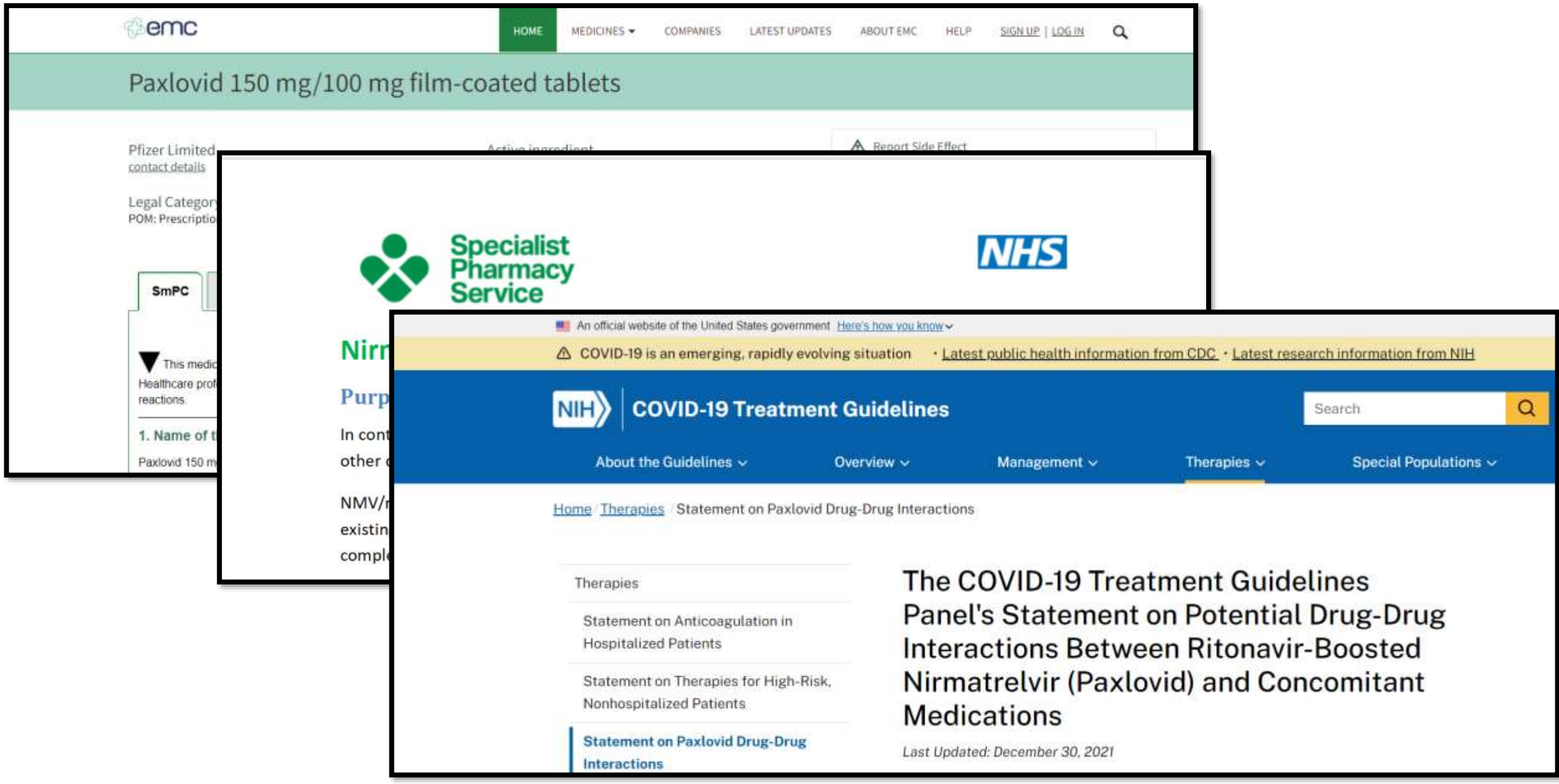
- Is a dose change the only way to manage the interaction?

- Can the drug be safely stopped?

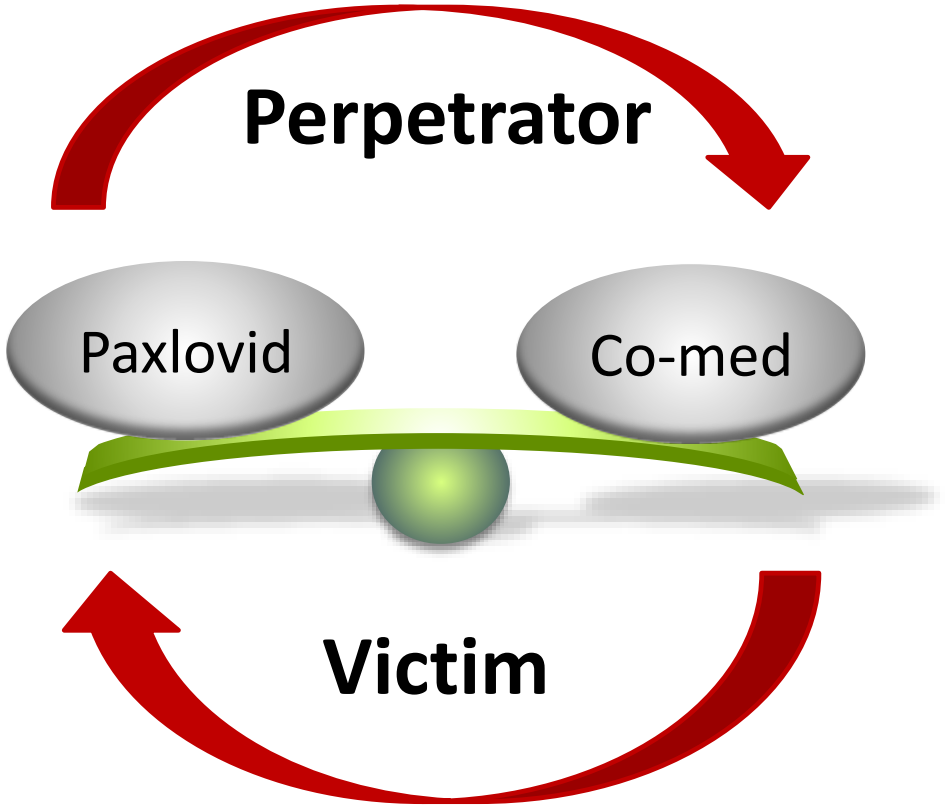
- Can we continue with the agent and ask the patient to monitor for side effects e.g. postural hypotension, dizziness etc for amlodipine and if it occurs, stop the drug for the remainder of the course?

- Can we provide information to manage e.g. extra contraception for a time period

Other resources



Case study examples



Liverpool Drug Interactions Group

Assessing a patient for Paxlovid (nirmatrelvir/ritonavir)

Produced 3 February 2022

Please check www.covid19-druginteractions.org for updates.

Data are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

Developed by Kirsteen Hill, ID/HIV/COVID Pharmacist, Dundee, Scotland and adapted by Liverpool Drug Interactions Group.

ANY OF THE FOLLOWING:

- **<18 years**
- **Pregnancy**
- **Severe renal impairment - eGFR (CrCl if >75years) <30 ml/min**
- **Severe liver disease - Child Pugh Class C**
- **Unable to swallow tablets**
- **Prescribed any medicines below:**

Amiodarone	Pethidine
Alfuzosin*	Phenobarbitone
Aliskiren	Primidone
Apixaban*	Pimozide
Bosentan	Phenytoin
Carbamazepine	Quetiapine
Ciclosporin	Ranolazine
Clozapine	Rifampicin
Clonazepam	Rivaroxaban*
Colchicine	Salmeterol*
Diazepam*	Sildenafil *(pulmonary hypertension)*
Disopyramide	Sirolimus
Domperidone*	St John's Wort
Dronedarone	Tacrolimus
Eplerenone	Tadalafil *(pulmonary hypertension)*
Flecainide	Ticagrelor
Ivabradine	
Lercanidipine*	
Midazolam (oral)	

**unless medicine can be stopped safely for 8 days*

Note: list of medicines not exhaustive and subject to change

YES

No Paxlovid

NO

Use covid19-druginteractions.org (or Paxlovid product label if medicine not listed) to check all medicines including:**

- OTC medicines
- Recreational drugs
- Hospital supplied medicines e.g.,
  - systemic anticancer treatment (SACT) within last 28 days
  - opiate substitution therapy
  - HCV/HBV/HIV treatment
  - hormonal contraceptives (except implant/depot)
  - steroid injections
  - depot antipsychotics
  - multiple sclerosis treatment

ANY RED/AMBER INTERACTIONS?

YES

- **Review full information on covid19-druginteractions.org and consider practicalities of advice/monitoring:**
  - Can medicine be withheld safely for 8 days? e.g., simvastatin
  - Can a dose adjustment be done easily? e.g., be aware of patients on compliance devices or those who do not have tablets/liquid to allow dose change, or if there is concern re patient understanding. Consider alternative day dosing if a dose change is impractical.
  - Can the patient be advised regarding which adverse reactions to be aware of and what to do?
- **Clinical decision (including consulting a specialist if appropriate) based on all the individual patient information and discussion with patient to prescribe Paxlovid.**

NO

No Paxlovid

** *No need to check medicines below on interaction website (list not exhaustive):*

ACE inhibitors
Acid reducing agents (antacids, PPIs, H2RAs)
Aspirin
Azathioprine
Beta Blockers
Corticosteroids (oral/inhaled/topical)
Fluvastatin
Furosemide
Gabapentin
HRT/Contraceptive implant or depot
Immunoglobulin
Inhalers (except salmeterol)
Insulin
Levothyroxine
Metformin
Methotrexate
Monoclonal antibodies (MABs)
Mycophenolate
NSAIDs (except piroxicam)
Pravastatin
Pregabalin

YES

eGFR (CrCl if >75 years) ≥60 ml/min

YES

✔ Paxlovid Full Dose

Nirmatrelvir 300 mg (2 x 150 mg) twice daily + Ritonavir 100 mg (1 tablet) twice daily for 5 days

NO

✔ Paxlovid ↓ Dose

Nirmatrelvir 150 mg (1 x 150 mg) twice daily + Ritonavir 100 mg (1 tablet) twice daily for 5 days

Liverpool COVID-19 Interactions (covid-druginteractions.org)

Case study 1: NR 33 year old female

Past medical history:
Rheumatoid arthritis
Asthma
Depression

Drug History:
Adalimumab 40mg SC fortnightly
Methotrexate 25mg SC once weekly
Folic acid 5mg once weekly
Venlafaxine XL 225mg OD
Relvar Ellipta® (Fluticasone furoate/vilanterol) 92/22 mcg 1 puff BD
Salbutamol Easyhaler® 100mcg 2 puffs PRN
Microgynon® (ethinylestradiol / levonorgestrel)

General guidance for patients with IMID – temporarily withhold DMARD (s), biologics and/or JAK inhibitor until antiviral course completed and symptoms are improving (~ 1 – 3 weeks)
→ Hold METHOTREXATE / ADALIMUMAB

COVID-19 Drug Interactions

UNIVERSITY OF LIVERPOOL

Drugs

nirm

A-Z Class Trade

- [x] Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
- [x] Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Co-medications

levon

A-Z Class

- [x] Adalimumab
- [x] Methotrexate (rheumatoid arthritis)
- [x] Fluticasone
- [x] Folic acid
- [x] Venlafaxine
- [x] Vilanterol
- [x] Levonorgestrel (COC)
- [x] Levonorgestrel (COC)

Drug Interactions

Check COVID/COVID drug interactions

Reset Checker

Switch to table view Results Key

Potential Interaction

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Levonorgestrel (COC)

More Info

Potential Weak Interaction

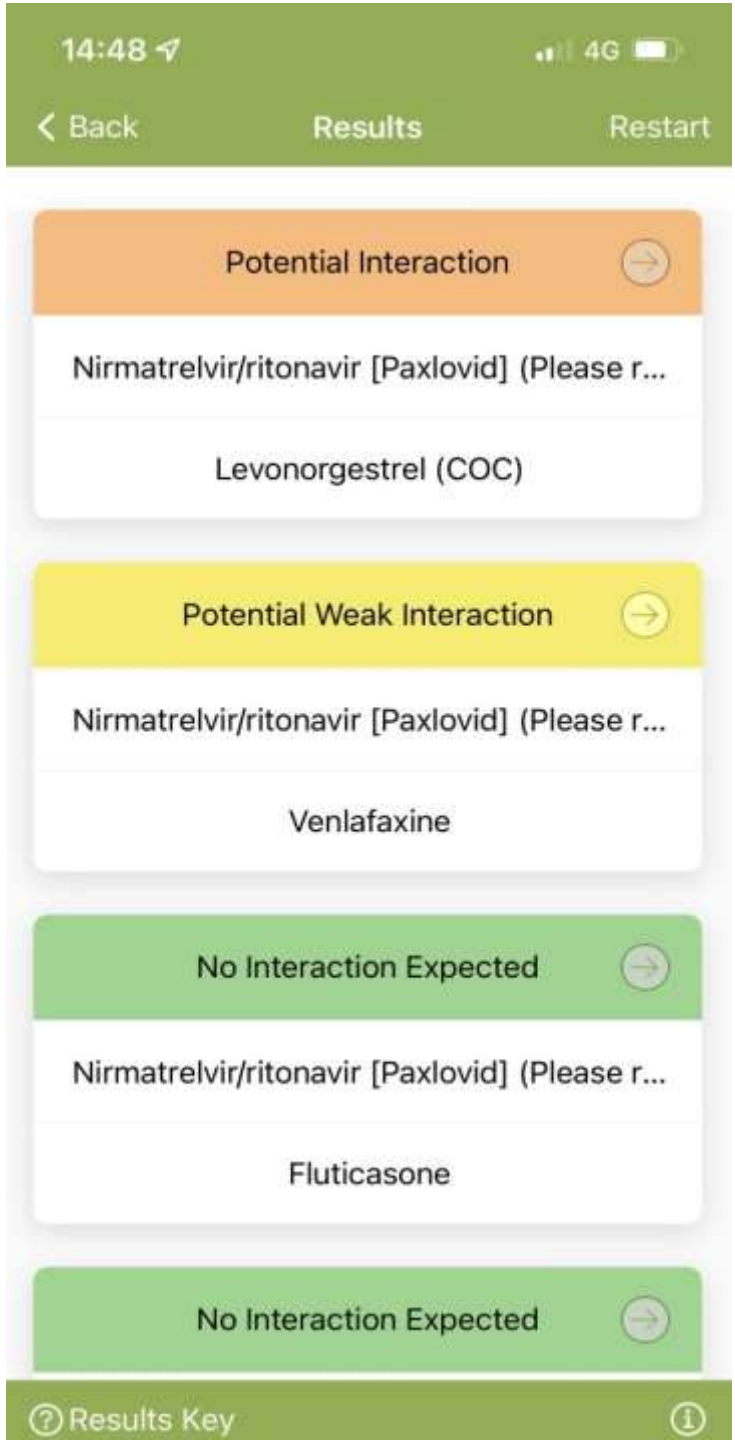
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Venlafaxine

COVID-19 Drug Interactions

UNIVERSITY OF LIVERPOOL

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Adalimumab	◆
Fluticasone	◆
Folic acid	◆
Levonorgestrel (COC)	■
Methotrexate (rheumatoid arthritis)	◆
Venlafaxine	▲
Vilanterol	◆



	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Adalimumab	◆
Fluticasone	◆
Folic acid	◆
Levonorgestrel (COC)	■
Methotrexate (rheumatoid arthritis)	◆
Venlafaxine	▲
Vilanterol	◆

Corticosteroids (inhaled/oral): Regular use of ritonavir can increase corticosteroid levels leading to risk of Cushing's

Low risk with 5 day course and no adjustment considered necessary for DDI

Exception: Triamcinolone (long half-life)

No Interaction Expected

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Fluticasone

Quality of Evidence: Very Low ⓘ

Summary:

Coadministration has not been studied. Fluticasone is metabolized by CYP3A4 and coadministration may therefore lead to elevated corticosteroid levels, Cushing's syndrome and adrenal axis suppression. Product labels for Paxlovid do not recommend coadministration due to the risk of Cushing's syndrome and adrenal axis suppression. However, given the short duration of nirmatrelvir/ritonavir treatment, this risk is considered to be low.

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Adalimumab	
Fluticasone	
Folic acid	
Levonorgestrel (COC)	
Methotrexate (rheumatoid arthritis)	
Venlafaxine	
Vilanterol	

Venlafaxine: mainly metabolized by CYP2D6 and to a lesser extent by CYPs 3A4, 2C19 and 2C9.

Ritonavir is weak inhibitor of CYP2D6 at a dose of 100 mg BD → Potential for <u>small</u> increase in venlafaxine levels but unlikely to be clinically relevant. No dose adjustment required.

Combined oral contraceptives

Potential Interaction

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Levonorgestrel (COC)

Quality of Evidence: Very Low

Summary:

Coadministration with a levonorgestrel-containing combined oral contraceptive (COC) has not been studied. Levonorgestrel is metabolized by CYP3A4 and is glucuronidated to a minor extent. Coadministration is predicted to increase levonorgestrel exposure. When used in combined pill, the estrogen component is expected to be reduced. This is unlikely to impair contraceptive efficacy, particularly considering the short duration of nirmatrelvir/ritonavir treatment, though it may increase the risk of irregular bleeding. However, it should be noted that the Paxlovid product labels state patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with nirmatrelvir/ritonavir, and until one menstrual cycle after stopping nirmatrelvir/ritonavir.

Liverpool COVID-19 Interactions (covid-druginteractions.org)

The COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

Last Updated: December 30, 2021

The EUA for ritonavir-boosted nirmatrelvir (Paxlovid) suggests that individuals who use products containing ethinyl estradiol for contraception should use a backup, nonhormonal contraceptive method because ritonavir-boosted nirmatrelvir (Paxlovid) has the potential to decrease ethinyl estradiol levels. However, the enzyme-inducing effects of ritonavir-boosted nirmatrelvir (Paxlovid) that would lead to lower hormone exposure are not expected to be clinically significant during 5 days of therapy and, therefore, would not be expected to decrease contraceptive effectiveness. In addition, ethinyl estradiol is always combined with a progestin for contraception. Progestin concentrations are expected to remain similar or increase when ritonavir-boosted nirmatrelvir (Paxlovid) is used concomitantly with combined hormonal contraception, which maintains the effectiveness of the oral contraceptive.

Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

Case study 1: NR 33 year old female

Past medical history:
Rheumatoid arthritis
Asthma
Depression

Drug History:
Adalimumab 40mg SC fortnightly
Methotrexate 25mg SC once weekly
Folic acid 5mg once weekly
Venlafaxine XL 225mg OD
Relvar Ellipta® (Fluticasone furoate/vilanterol) 92/22 mcg 1 puff BD
Salbutamol Easyhaler® 100mcg 2 puffs PRN
Microgynon® (ethinylestradiol / levonorgestrel)

Management plan:
Methotrexate/Adalimumab held as per recommended management of patients with IMID and COVID-19
No other changes to medication required
Consider additional contraceptive advice

Case study 2: CD 75 year old male

Past medical history:
Cirrhosis
Diabetes
Hypothyroidism
CVA (2006)

Drug History:
Metformin 1g BD
Simvastatin 40mg OD
Levothyroxine 150mcg OD
Amlodipine 10mg OD
Lisinopril 10mg OD
Aspirin 75mg OD

Most recent bloods:

LFTs
Bilirubin: 8 (< 20 umol/L)
ALT 67 (< 50 U/L)
AST 96 (< 40 U/L)
Alkaline Phosphatase 74 (30 – 130 U/L)
Albumin 35 (35 – 50 g/L)

U+Es normal

FBC
Hb 144 (115 – 165 g/L)
Platelets 139 (150 – 410 x 10^9/L)

Coag normal

No indication of advanced decompensated cirrhosis

NB Paxlovid® contraindicated with severe hepatic impairment (Child's Pugh C)

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Amlodipine	
Aspirin (Anti-platelet)	
Levothyroxine	
Lisinopril	
Metformin	
Simvastatin	

Levothyroxine: partly metabolised via glucuronidation. Case reports of hypothyroidism with regular ritonavir (4 weeks +)

Induction of glucuronidation takes several days → clinically relevant effect unlikely in 5 days

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Amlodipine	
Aspirin (Anti-platelet)	
Levothyroxine	
Lisinopril	
Metformin	
Simvastatin	

Amlodipine: 2-fold increase in amlodipine exposure predicted

Consider reduction of amlodipine dose by 50% → may be difficult to do in practice

Options:

- Advise patient to be aware of symptoms of hypotension and pause treatment if symptomatic
- Consider withholding amlodipine for 8 days

Consider similar management strategies for other calcium channel blockers

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Amlodipine	
Aspirin (Anti-platelet)	
Levothyroxine	
Lisinopril	
Metformin	
Simvastatin	

Simvastatin: ↑↑ levels increasing risk of myopathy → AVOID

But, for most patients, statins can be safely withheld for short duration

Other statins?

STOP

- ☒ **Lovastatin**
- ☒ **Atorvastatin**
- ☒ **Rosuvastatin**

CONTINUE

- ☑ **Fluvastatin**
- ☑ **Pitavastatin**
- ☑ **Pravastatin**

Case study 2: CD 75 year old male

Past medical history:
Cirrhosis
Diabetes
Hypothyroidism
CVA (2006)

Drug History:
Metformin 1g BD
Simvastatin 40mg OD
Levothyroxine 150mcg OD
Amlodipine 10mg OD
Lisinopril 10mg OD
Aspirin 75mg OD

Management plan:

Continue:
Aspirin
Metformin
Levothyroxine
Lisinopril

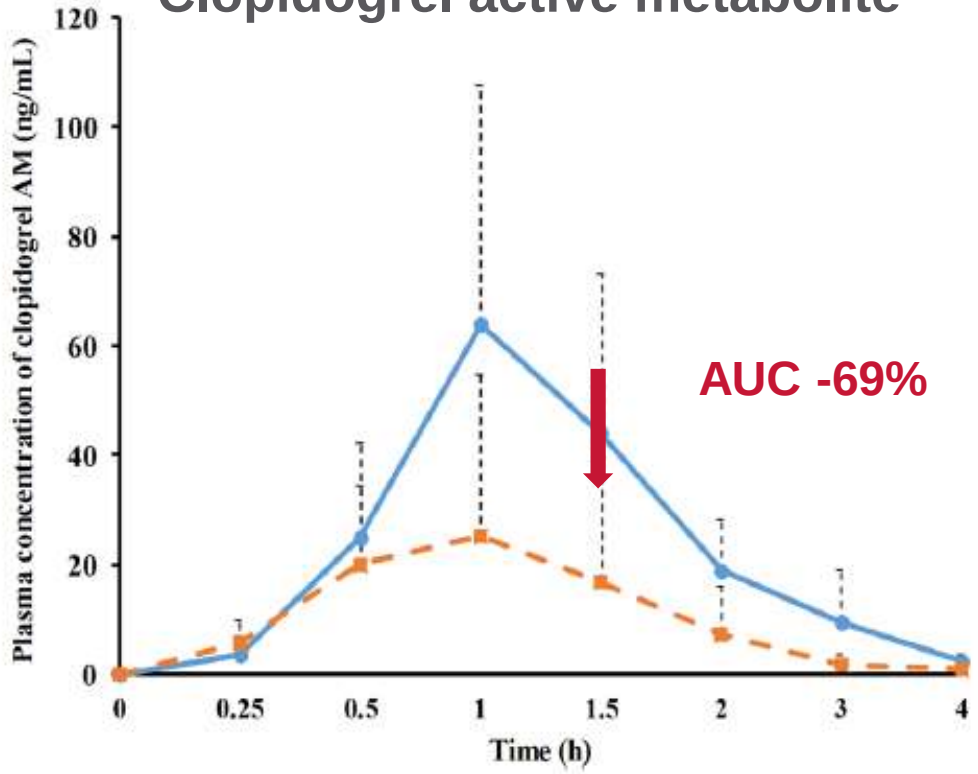
Hold:
Simvastatin
Amlodipine

Highlight to patient importance of re-starting medication **3 days** after Paxlovid® course complete

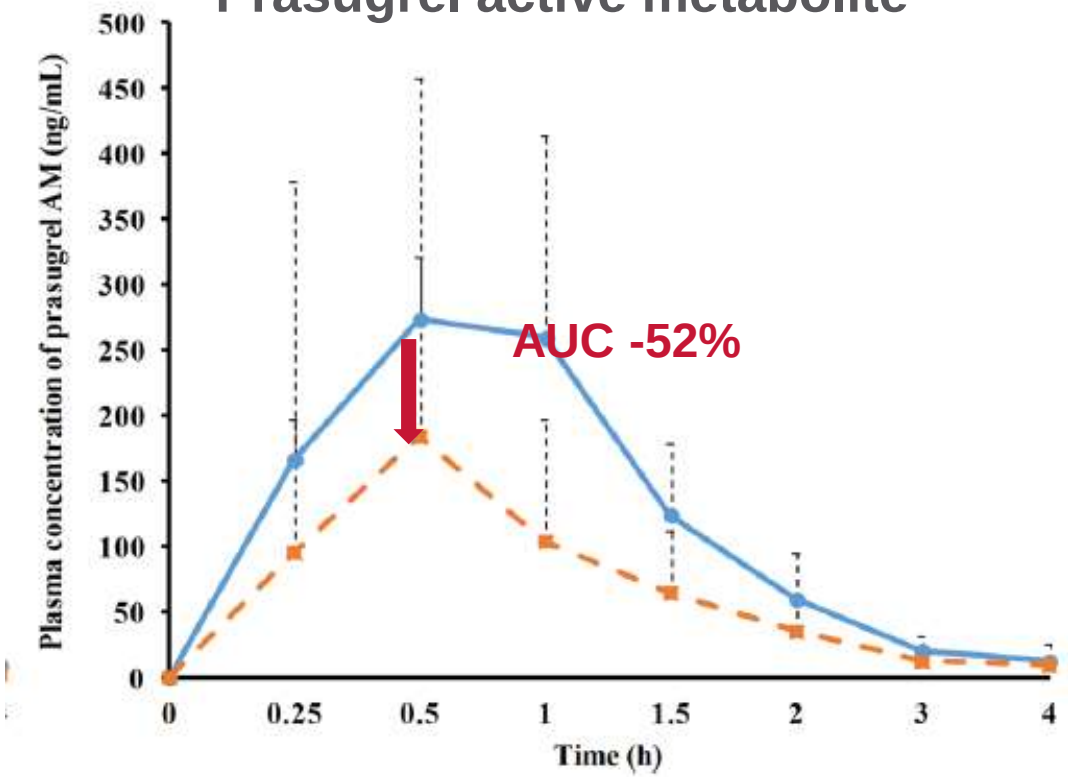
Clopidogrel or prasugrel with ritonavir/cobicistat: Pharmacokinetic effect

Open label, randomised, cross over study comparing pharmacokinetics and platelet inhibition of loading doses of clopidogrel and prasugrel in PLHIV (n=9) receiving ritonavir or cobicistat based ART to healthy volunteers (n=12)

Clopidogrel active metabolite



Prasugrel active metabolite



Antiplatelet drug alone — — — Antiplatelet drug + Ritonavir/Cobicistat boosted ARV

Active metabolites of clopidogrel and prasugrel are significantly reduced by ritonavir and cobicistat

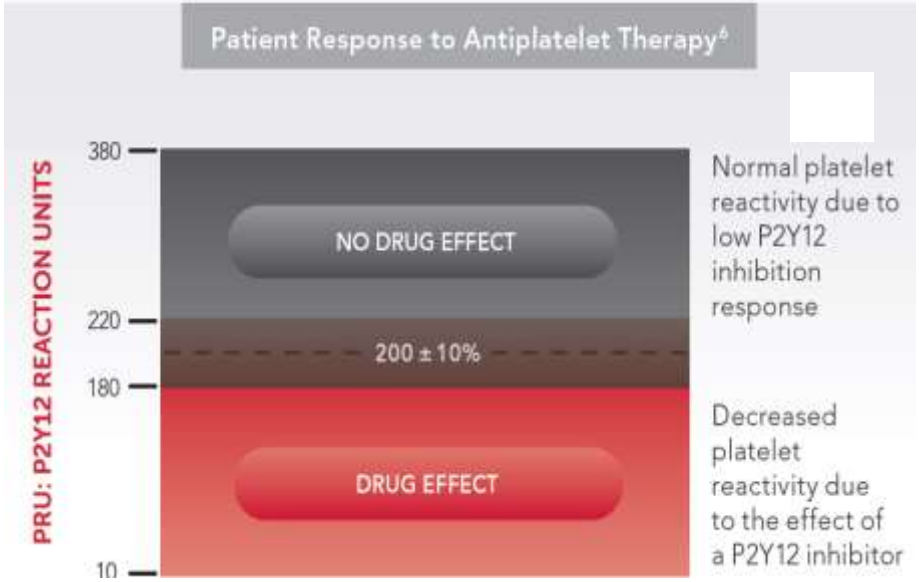
AUC, area under the curve, PRU, platelet reactivity units.

Marsousi N et al. Clin Pharmacokinet 2018

Clopidogrel or prasugrel with ritonavir/cobicistat: Pharmacodynamic effect

Open label, randomised, cross over study comparing pharmacokinetics and platelet inhibition of loading doses of clopidogrel and prasugrel in PLHIV (n=9) receiving ritonavir or cobicistat based ART to healthy volunteers (n=12)

Platelet receptor blockade measured with VerifyNow®



www.accriva.com

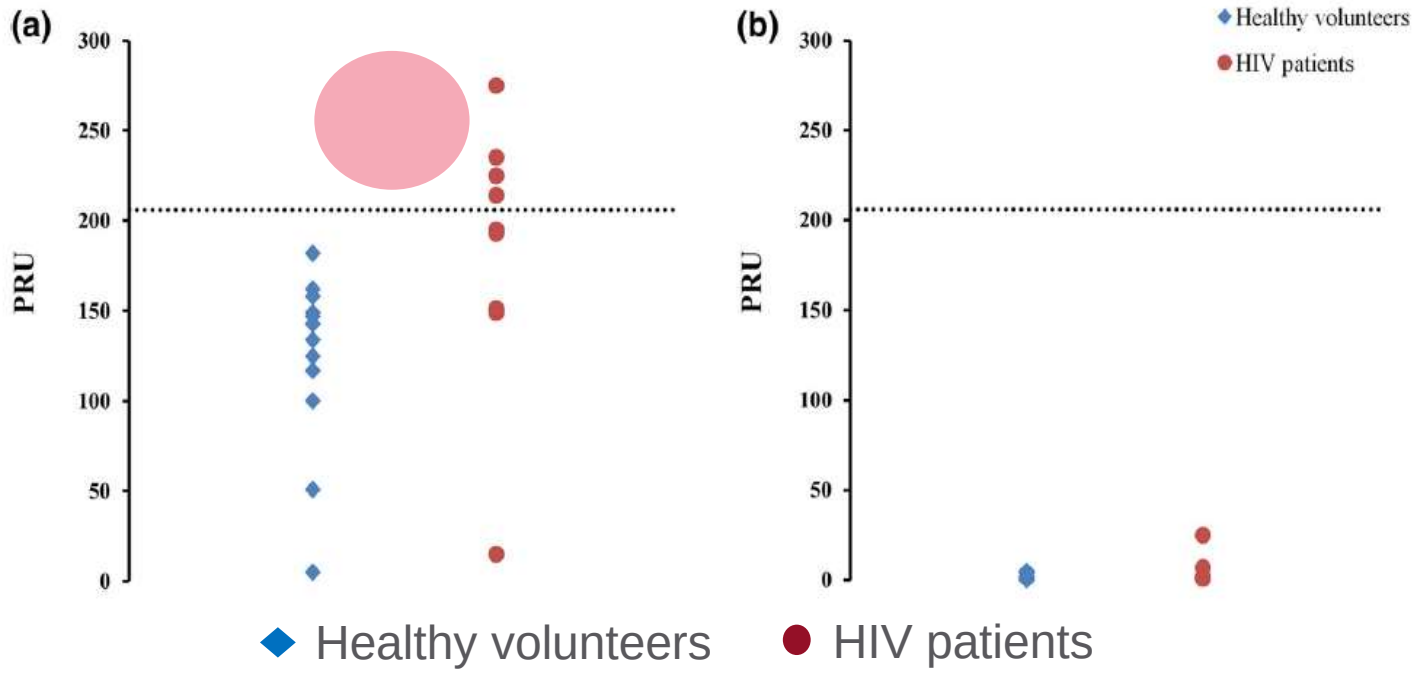
<200 P2Y12 Reaction Units (PRU) suggests P2Y12 inhibition effect

Clopidogrel

44% HIV patients did not achieve platelet inhibition

Prasugrel

All HIV patients prasugrel platelet inhibition remains adequate



Prasugrel should be preferred over clopidogrel in presence of boosted regimens when possible

PRU, platelet reactivity units.

Marsousi N et al. Clin Pharmacokinet 2018

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Clopidogrel	
Clopidogrel (recently stented patients)	

High risk patients (e.g. initial period (at least 6 weeks) post coronary stenting → AVOID

Other clinical indications (e.g. alternative to aspirin due to intolerance) where transient loss of efficacy may be acceptable → CONTINUE

Case study 3: MB 39 year old female

Past medical history:

Down's syndrome
Epilepsy

Drug History:

Carbamazepine 400mg BD
Levetiracetam 1g BD
Omeprazole 20mg OD
Ibuprofen 400mg PRN

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Carbamazepine	
Ibuprofen	
Levetiracetam	
Omeprazole	

Carbamazepine is a potent CYP3A4 inducer

Coadministration

- nirmatrelvir Cmax and AUC ↓ 43% and 55%

Offset of enzyme induction takes ~ 2 weeks therefore an **alternative COVID-19 therapy is required**

Case study 4: BH 57 year old male

Past medical history:

HIV
Schizophrenia
Previous IV drug use

Drug History:

Triumeq® (Dolutegravir/Abacavir/Lamivudine) 1 tab daily

Quetiapine 200mg BD

Methadone 110mg daily

	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Dolutegravir/Abacavir/ Lamivudine	
Methadone	
Quetiapine	

Majority of HIV antiretrovirals can be given with Paxlovid®

Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment with no dosage modification. Patients should be informed about the potential occurrence of adverse effects (i.e. gastro-intestinal due to the higher dose of ritonavir)

Do Not Coadminister

Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)

Quetiapine

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied but is not recommended. Quetiapine is primarily metabolised by CYP3A4 and coadministration with ketoconazole (a CYP3A4 inhibitor) increased quetiapine AUC by 5-8 fold. The European product label for quetiapine contraindicates quetiapine with CYP3A4 inhibitors (such as ritonavir). However, the US product label recommends that quetiapine should be reduced to one sixth of the original dose if coadministered with a potent CYP3A4 inhibitor. The decision to modify the dosage should be done in consultation with a specialist in mental health medicine as it could destabilize a patient. Given the mechanism-based inhibition of nirmatrelvir/ritonavir, the adjusted dose of quetiapine would have to be maintained up to 3 days after the last dose of nirmatrelvir/ritonavir. Similarly, if it is decided to pause quetiapine during nirmatrelvir/ritonavir treatment, quetiapine would have to be resumed 3 days after the last dose of nirmatrelvir/ritonavir.

Potential 5 – 8 fold increase in quetiapine
Contraindicated in European product information

FDA EUA: If coadministration necessary, reduce dose to 1/6th of original daily dose

→ Is this practical / feasible in non-hospitalised patients?
Risk of destabilisation of mental health – discussion with psychiatry team

Drugs not listed on covid-druginteractions.org website or in SPS guidance?

www.hep-druginteractions.org
Check Ombitasvir/paritaprevir/r(itonavir)

www.hiv-druginteractions.org
Check ritonavir (or ritonavir-containing regimens)

NB:
Long-term use may change the potential for interaction

Product label for Paxlovid® and co-medication
- Is the co-med a CYP3A4/P-gp substrate?
- Is the co-med a CYP inducer?

Local blood-borne virus pharmacy team

Local medicines information service

covidpk@liverpool.ac.uk

Other national guidelines:
www.covid19treatmentguidelines.nih.gov
Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)

Key learning points

- Paxlovid (nirmatrelvir/ritonavir) is the most effective oral treatment option for patients with mild to moderate COVID-19 to reduce the risk of hospitalisation or death

- Individualised patient assessment and clinical decision making key to ensuring as many patients as possible can receive treatment in their own home

- Potential for drug interactions exist **but** most interactions can be manageable with available tools and resources

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