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LIVERPOOL MASTERCLASS IN ANTIVIRAL PHARMACOLOGY

B Cell depleted patients and Paxlovid

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Disclosures

- Honoraria and/or research grants from Viiv, Gilead, MSD

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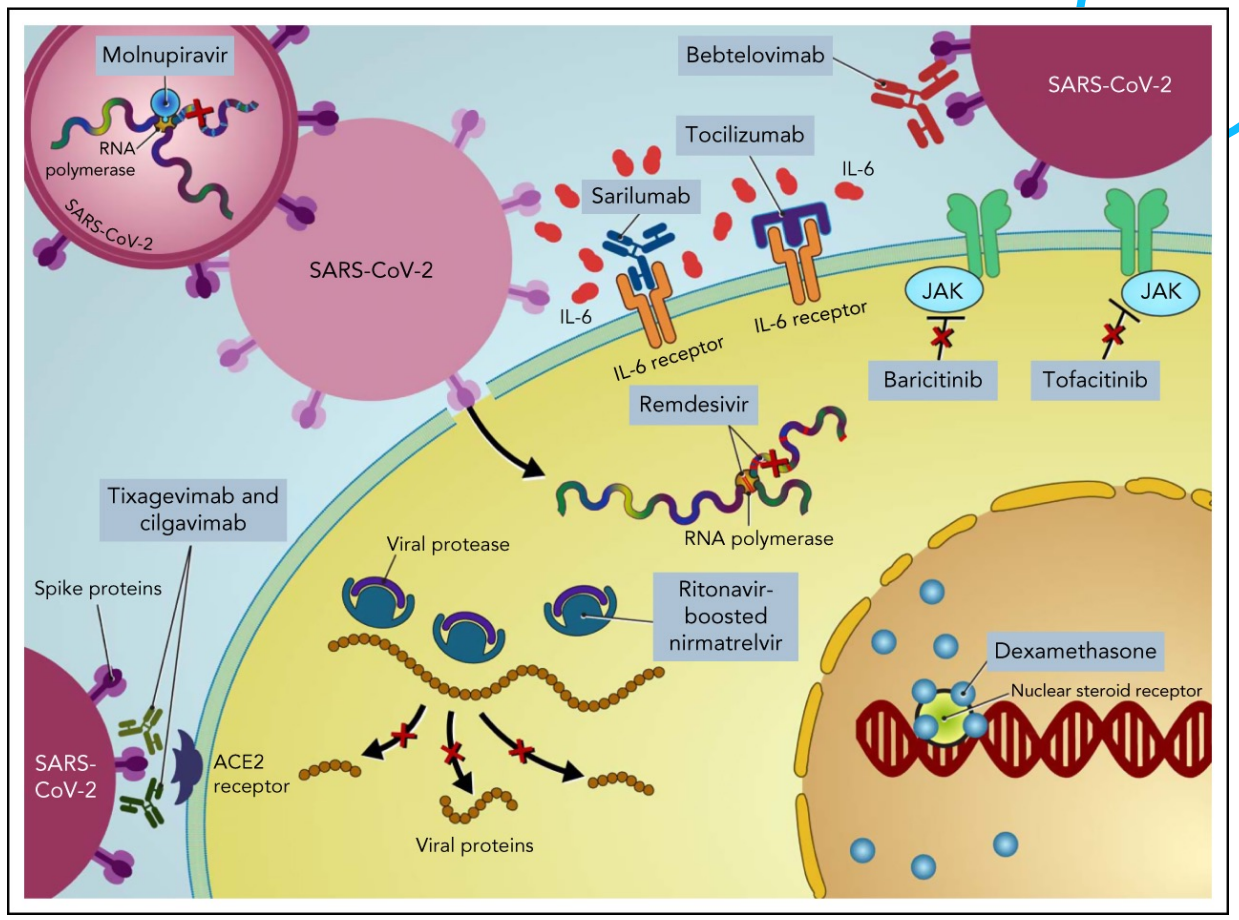
PAXLOVID (Nirmatrelvir + Ritonavir)?

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



Firas El Chaer,Jeffery J. Auletta,Roy F. Chemaly, Blood, 2022

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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, CYP2B6, CYP2C9, CYP2C19 and UGT

Inhibition interactions by ritonavir can occur in 24-48 hours: **SIGNIFICANT** FOR PAXLOVID 5 DAYS

Induction interactions by ritonavir take up to 14 days: **NOT SIGNIFICANT** FOR PAXLOVID 5 DAYS

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.

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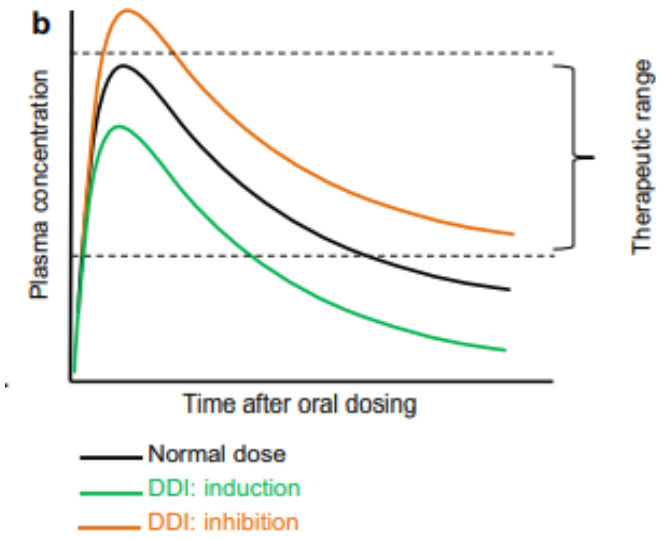
What is a Clinically Significant Interaction?

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?

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Taking a drug history

Check ALL medicines:

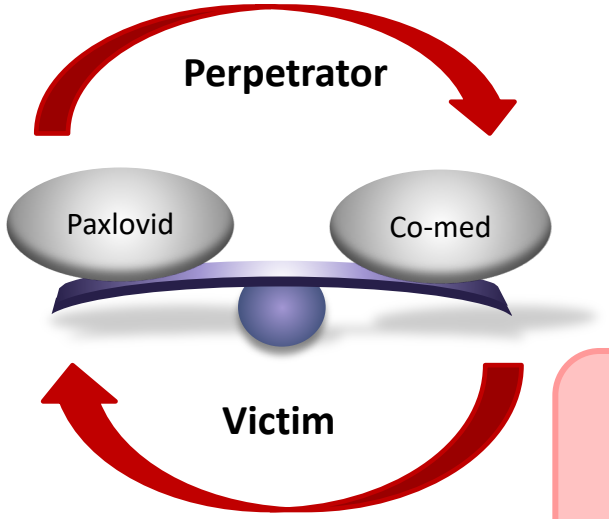
- OTC
- Recreational drugs
- Hospital supplied such as:
  - SACT
  - OST
  - HCV/HIV/HBV treatment
  - Contraception
  - Steroid Injections
  - Depot antipsychotics

Multimorbidity

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

'Polydoctory'

DDIs



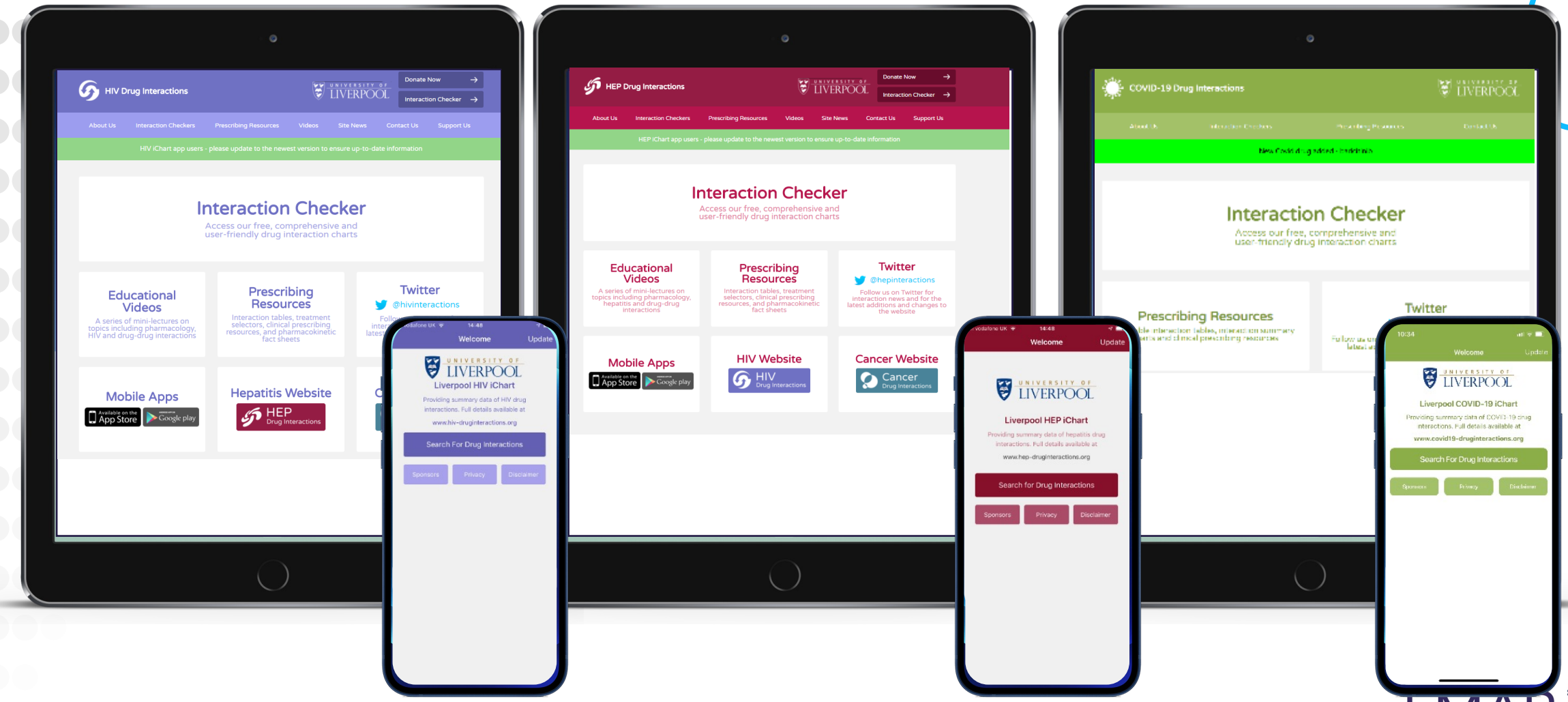
Reduced efficacy of agent?

Reduced efficacy of co-medication?*

Adverse effect?

Age-related Pharmacokinetic & Pharmacodynamic change

DDI Resources – Apps and desktop versions



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

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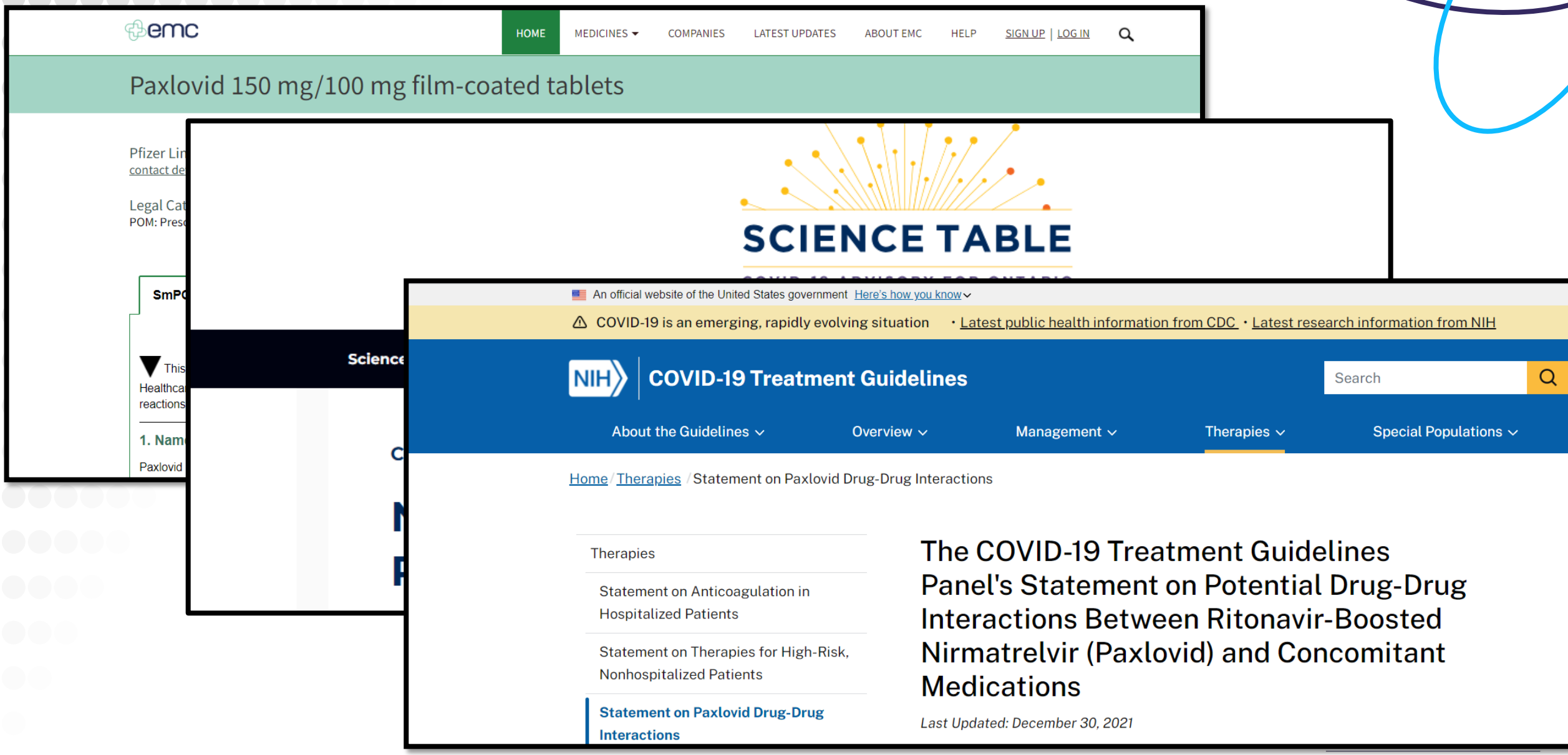
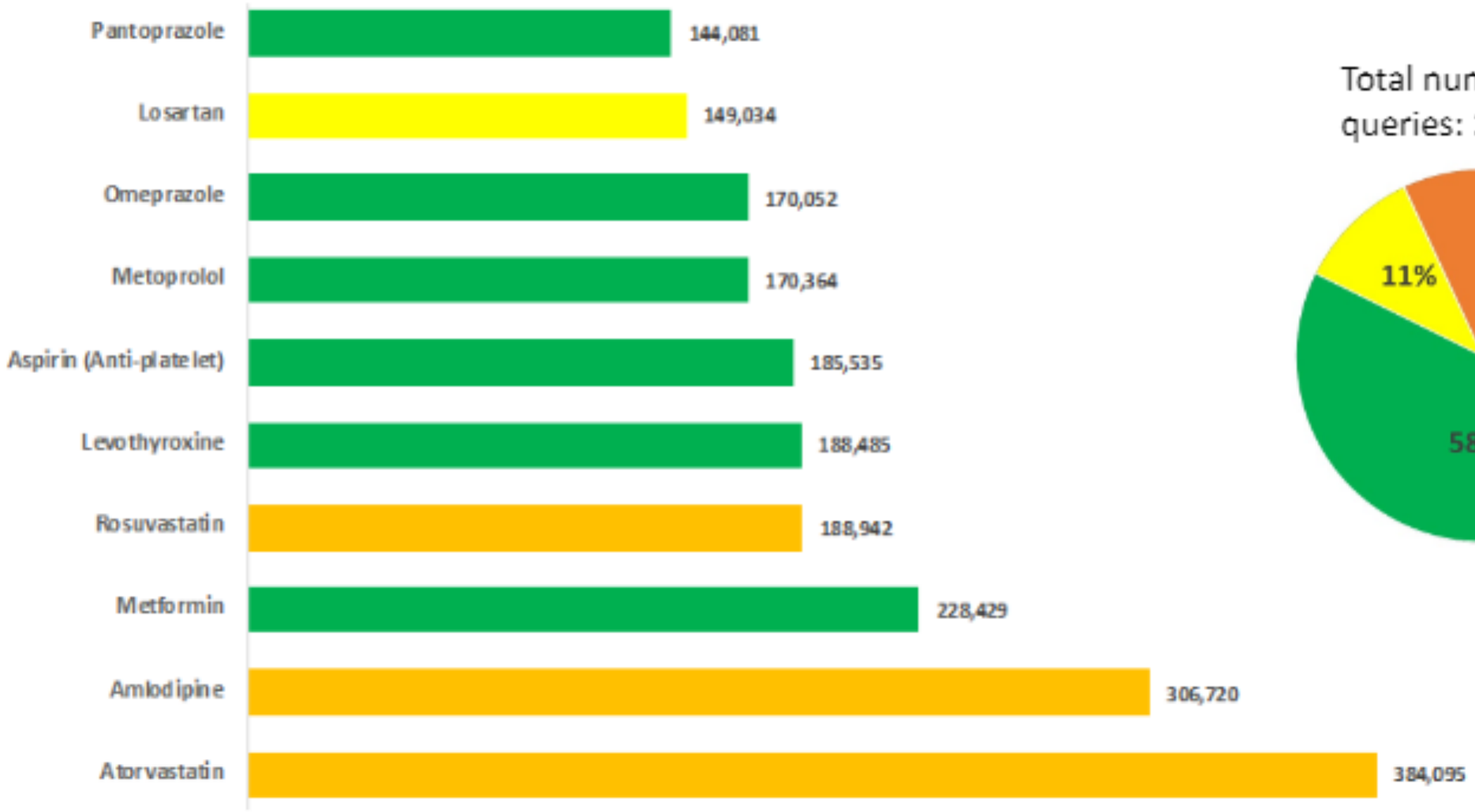
Other resources

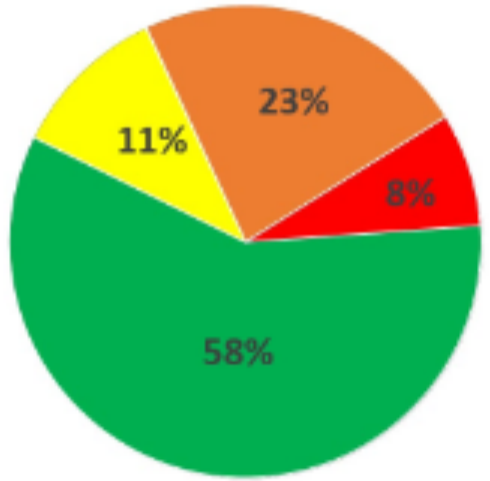


Top most searched comedications with nirmatrelvir/ritonavir globally

Drug-drug interaction queries from February 1, 2022 to August 15, 2023



Total number of queries: **10'515'177**



www.covid19-druginteractions.org google analytics

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? 5 days vs 10 days +

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.

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B Cell depleted patients

Anti-CD20 antibody (aCD20)-based B cell-depleting strategies such as rituximab are widely used in B cell hematologic malignancies and across a variety of autoimmune disorders:

- B cell depletion occurs within 72 hours
- Normal B cells obtained 9-12 months after treatment
- Poor response to covid vaccination
- aCD20-related impairment of adaptive immunity means time to viral clearance significantly prolonged compared.
- Case series indicate PCR positivity over >80 days in some B Cell treated patients
- Longer courses of Nirmatrelvir/r +/- additional agents may be required

Furlan A, Forner G, Cipriani L, Vian E, Rigoli R, Gherlinzoni F, et al. Dramatic Response to Convalescent Hyperimmune Plasma in Association With an Extended Course of Remdesivir in 4 B Cell-Depleted Non-Hodgkin Lymphoma Patients With SARS-Cov-2 Pneumonia After Rituximab Therapy. *Clin Lymphoma Myeloma Leuk*. 2021

Case study patient 1

- 47 female treated with Rituximab-Bendamustine for Stage IVb follicular lymphoma
- May: Dry cough and ground glass changes on staging CT.
  - Nose and throat swabs PCR positive for SARS-CoV-2
- Treated with 10 days of remdesivir and dexamethasone.
- Readmitted 2 months later with fever and persistent SoB
- Remained PCR positive
- Stabilised and retreated with remdesivir and nirmatrelvir/r for 14 days as outpatient

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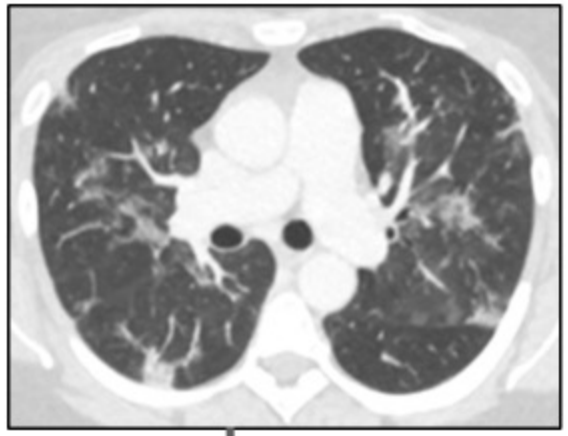
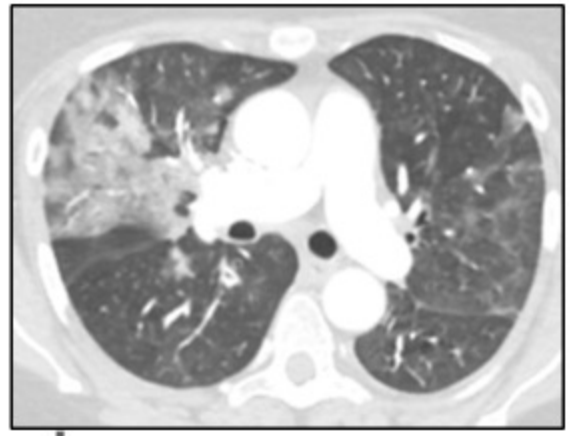
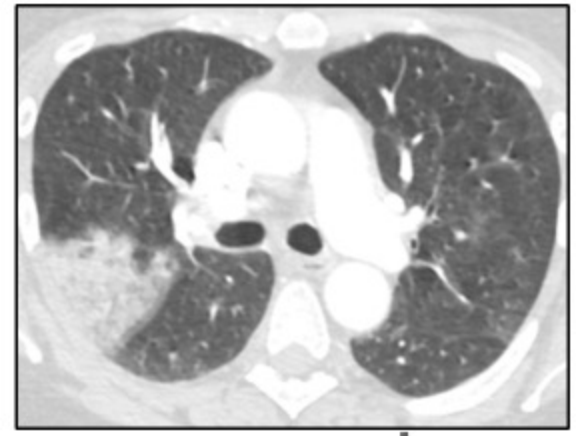
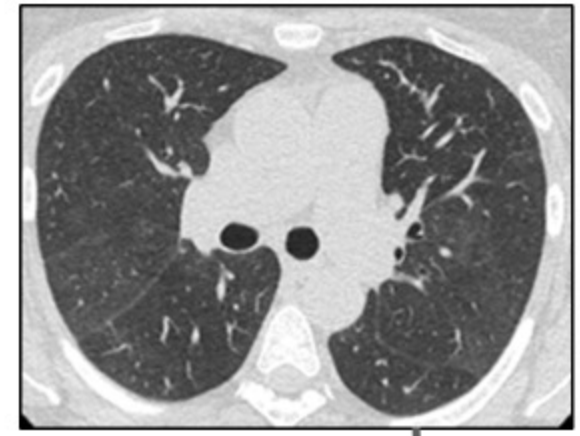
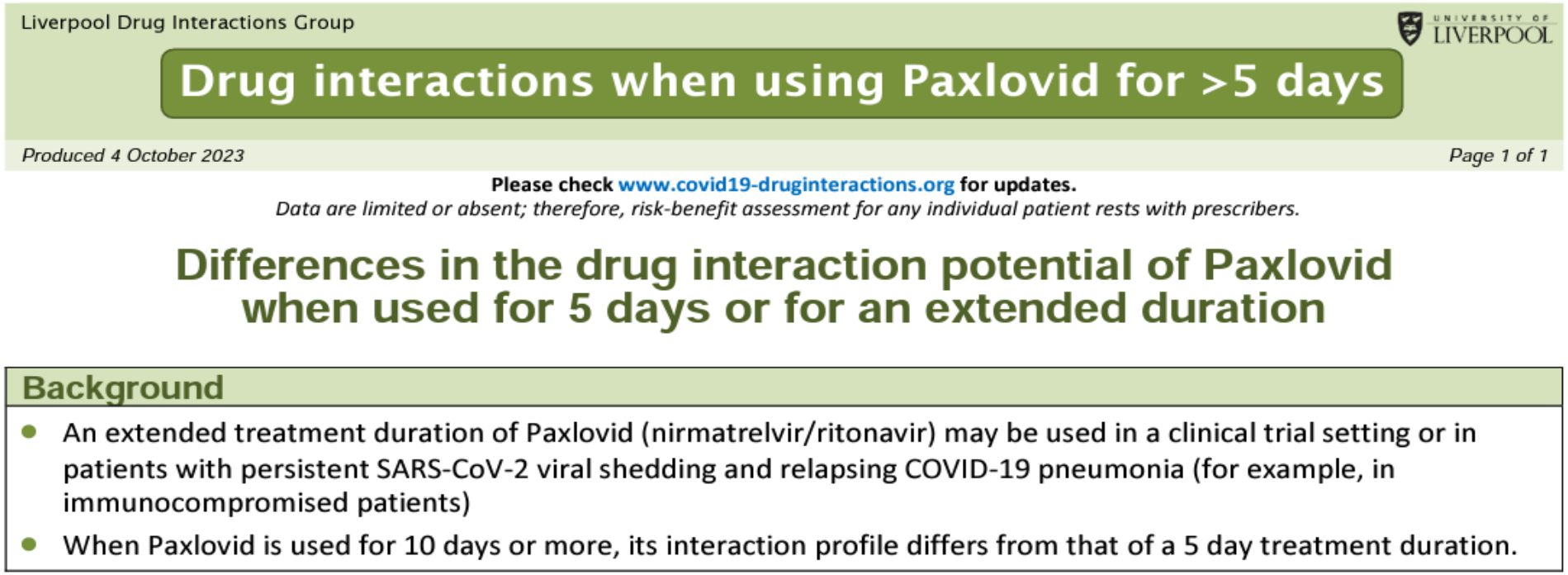





	19 MAY	10 JUN	14 JUN	17 JUN	18 JUN	22 JUN	24 JUN	29 SEP	6 OCT	10 OCT	15 OCT	30 OCT	11 NOV
Nose & throat swab	★	-	-							-	-	-	-
Plasma				★		★		★	★	-	-	-	-
BAL					★						-	-	-
Faeces						★							
Viral Culture				Viable virus cultured									
Treatment					RDV & DEX	RDV & DEX	RDV & DEX	RDV+ PAX	RDV +PAX	RDV + PAX			

Managing longer term interactions with Paxlovid



Liverpool Drug Interactions Group

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Drug interactions when using Paxlovid for >5 days

Produced 4 October 2023

Page 1 of 1

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

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

Differences in the drug interaction potential of Paxlovid when used for 5 days or for an extended duration

Background

- An extended treatment duration of Paxlovid (nirmatrelvir/ritonavir) may be used in a clinical trial setting or in patients with persistent SARS-CoV-2 viral shedding and relapsing COVID-19 pneumonia (for example, in immunocompromised patients)
- When Paxlovid is used for 10 days or more, its interaction profile differs from that of a 5 day treatment duration.

- Induction of CYPs (CYP 1A2, CYP 2BC, CYP2C9, CYP2C19) and UGTs by ritonavir may result in a clinically significant interaction
- Pausing medications for longer durations may have more risk of harm

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What medications are affected?

Examples of comedications with potentially clinically relevant interactions

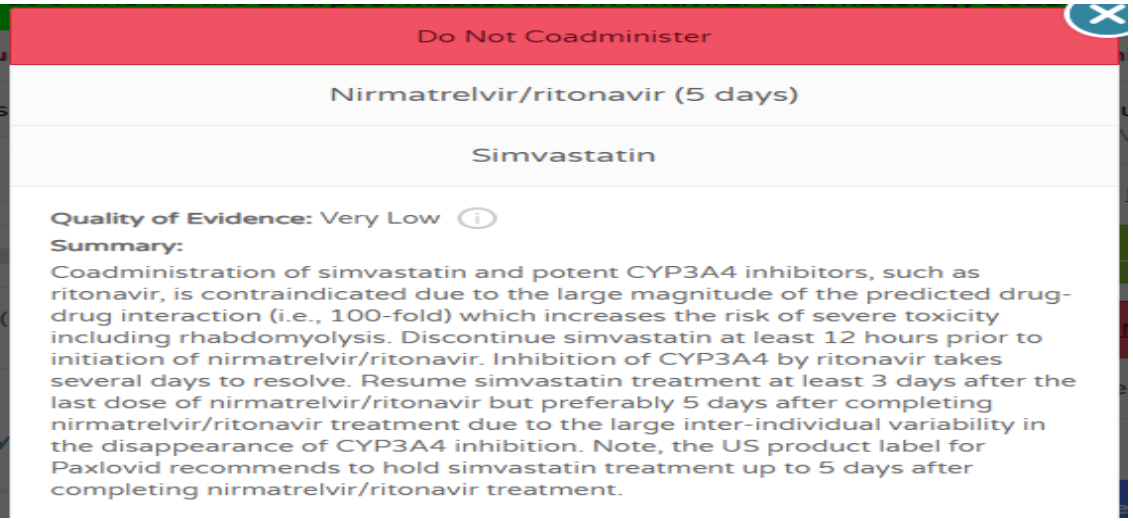
- The list below gives examples of drugs which may have a potentially significant interaction due to enzyme induction by ritonavir when Paxlovid is given for an extended duration.

Artesunate (UGT)
Asenapine (UGT1A1/CYP1A2)
Acenocoumarol (CYP2C9/1A2/2C19)
Agomelatine (CYP1A2)
Aminophylline (CYP1A2)
Artemether (UGT)
Atovaquone (UGT)
Binimetinib (UGT1A1)
Bupropion (CYP2B6)
Abrocitinib (CYP2C19/2C9)
Canagliflozin (UGT1A9/2B4)
Cyclophosphamide (CYP2B6>2C9, 3A4)
Dabigatran (P-gp)
Dacarbazine (CYP1A2)
Dexmedetomidine (UGT)
Dipyridamole (UGT1A)
Dronabinol (CYP2C9>3A4)
Eltrombopag (UGT1A1/CYP1A2)
Epirubicin (UGT2B7)
Febuxostat (CYP1A2/UGT)
Frovatriptan (CYP1A2)
Gliclazide (CYP2C19)
Glimepiride (CYP2C9)
Glipizide (CYP2C9)
Hydromorphone (UGT2B7)
Isavuconazole (CYP3A4/UGT)
Lamotrigine (UGT1A4)
Letermovir (UGT1A1)
Levothyroxine (UGT)
Minoxidil (UGT)
Moxifloxacin (UGT1A1)
Mycophenolate (UGT)
Olanzapine (CYP1A2)
Oxprenolol (UGT)
Rasagiline (CYP1A2)
Ropinirole (CYP1A2)
Pirfenidone (CYP1A2)
Pizotifen (UGT2B10)
Prazosin (CYP/UGT)
Proguanil (CYP2C19>3A4)
Sertraline (CYP2B6>2C9/2C19)
Siponimod (CYP2C9>3A4)
Sodium valproate (UGT/CYP2C9)
Phenprocoumon (CYP2C9/3A4)
Theophylline (CYP1A2)
Ticlodipine (CYP2B6/2C19/1A2 + other CYPs)
Tolbutamide (CYP2C9/2C8/2C19)
Triamterene (CYP1A2)
Valproate semisodium (UGT/CYP2C9/2C19)
Valproic acid (UGT/CYP2C9/2C19)
Warfarin (CYP1A2/CYP2C9/3A4)

www.covid19-druginteractions.org/prescribing_resources/paxlovid-extended-duration

Co-medications

- Olanzapine 10ng nocte
- Simvastatin 40mg nocte
- Omeprazole 20mg od



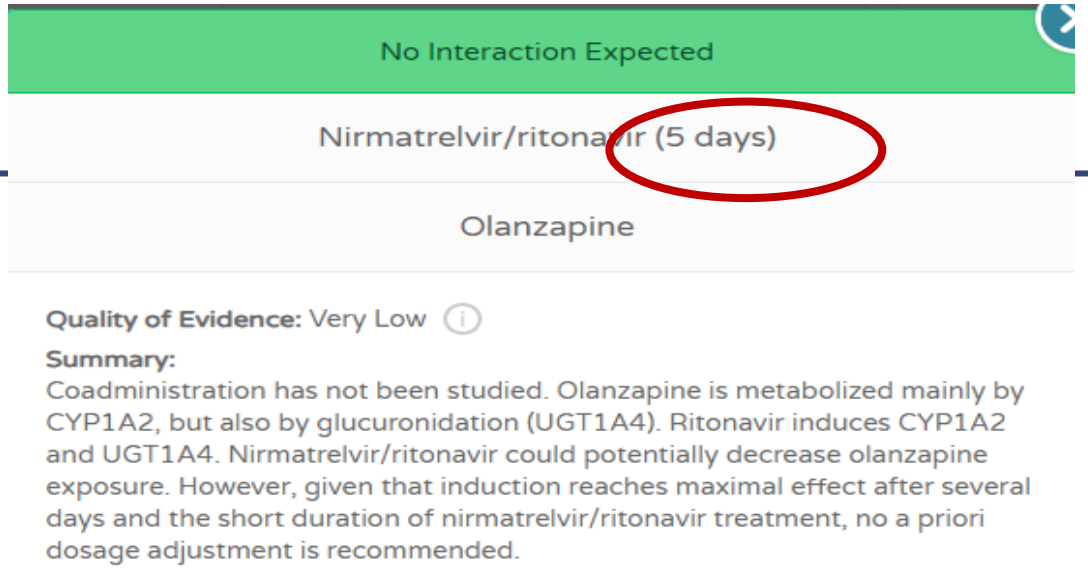
Other statins?

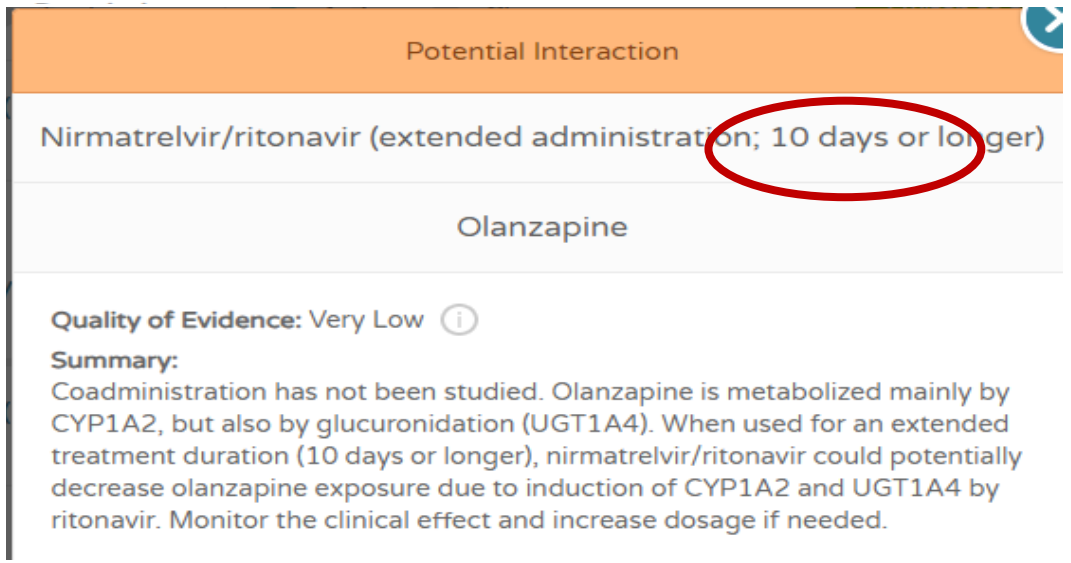
STOP

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

CONTINUE

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





Managing DDIs – considering individual risk–benefits

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 !

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Managing DDIs – considering individual risk–benefits

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Case study patient 2- 57 year old male

2013 Follicular lymphoma- remission
2018: Plasmablastic lymphoma: o-bendamustine (Aug 2019) and obinutuzumab (last infusion October 2021).
2021: high BP and started on amlodipine 10mg and fluticasone nasal spray for allergies

30/4/22: Tested positive for SARS-CoV2 (omicron).
- Developed type 1 respiratory failure: high flow nasal oxygen and dexamethasone and remdesivir.
- Recovered and discharged home, although a nasal PCR for SARS-COV-2 remained positive.

Case study patient 2- 57 year old male

- 10/8/22: readmitted and deteriorated again with type 1 respiratory failure and subsequently remained in hospital for 3 months requiring 3 admissions to the High Dependency Unit for respiratory support.
- Continued positive test by nasopharyngeal swab for SARS-CoV-2 with low CT values and was treated with remdesivir and dexamethasone.
- discharged home in December 2022.

In light of profound immunosuppression and multi-centre MDT discussion:

- 3 months of intravenous immunoglobulin (30mg every 3 weeks, Nov 2022 - Jan 2023) and paxlovid
- Remains PCR negative

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

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

- Half Amlodipine dose
- Monitor BP

COVID-19 Drug Interactions

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Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

Results Key

	Nirmatrelvir/ritonavir (5 days)	Nirmatrelvir/ritonavir (extended administration; 10 days or longer)
Fluticasone	◆	▲

↑↑

Potential Weak Interaction

Nirmatrelvir/ritonavir (extended administration; 10 days or longer)

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. The European product label for Paxlovid (5 day administration) does not recommend coadministration due to the risk of Cushing's syndrome and adrenal axis suppression; however, the American product label states this risk is low with short-term use of a strong CYP3A4 inhibitor. A retrospective review of published case reports of individuals developing a Cushing's syndrome while treated concurrently with a boosted HIV protease inhibitor and inhaled corticosteroids indicated that this adverse effect tended to occur after several months (and more rarely 2 weeks) of concurrent administration of these drugs. Therefore, the risk of developing a Cushing's syndrome is expected to be low when nirmatrelvir/ritonavir is used for an extended treatment duration (10 days or longer. However, prescribers should be aware of and to look out for signs of systemic corticosteroid side effects.

Conclusions

- Immunosuppression is a heterogenous group with distinct immunopathology and clinical response
- As vaccine response remains suboptimal, particularly in those b cell depleted, these patients remain to be complex and difficult to treat
- Longer courses of nirmatrelvir/ritonavir can be considered but drug interaction propensity needs considered and can differ from 5 day licensed courses

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COVID-19 Drug Interactions

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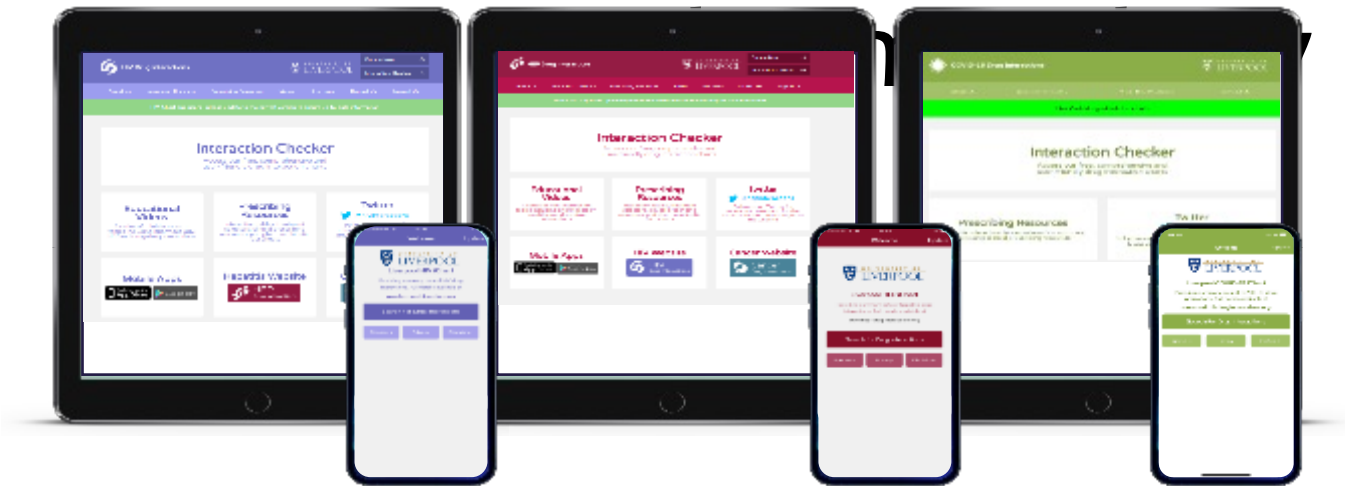

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