

Duration of CYP3A4 Inhibition after Stopping Paxlovid

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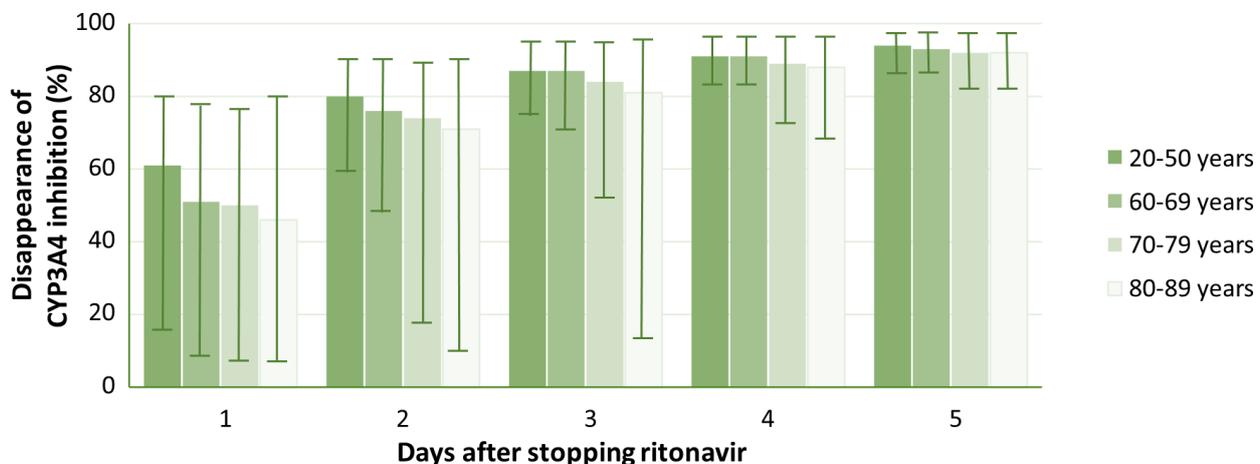
Please check www.covid19-druginteractions.org for updates.

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

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 suggest that over 80% of CYP3A4 inhibition will significantly have resolved 3 days after stopping ritonavir in most young and elderly individuals ^{2,3}. However, significant inter-individual variability should be highlighted as a few individuals may have a slower disappearance of CYP3A4 inhibition (see figure) ¹⁻³. 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 time window 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.

References

1. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using a limited sampling strategy. Katzenmaier S, Markert C, Riedel KD, *et al.* *Clin Pharmacol Ther.* 2011; 90:666-672.
2. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. Stader F, Khoo S, Stoeckle M, *et al.* *J Antimicrob Chemother.* 2020; 75(10):3084-3086.
3. Recommendations for the management of drug-drug interactions between the COVID-19 antiviral nirmatrelvir/ritonavir (Paxlovid) and comedications. Marzolini C, Kuritzkes DR, Marra F, *et al.* *Clin Pharmacol Ther* 2022 [epub ahead of print].