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.
- 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.
- Modelling data have shown that CYP3A4 inhibition significantly resolves 3 days after stopping ritonavir in most young and elderly individuals. However, the inter-individual variability should be highlighted as a few individuals may have a slower disappearance of CYP3A4 inhibition. 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.

References