

Recommendations for CNI/mTOR Management with Paxlovid Coadministration

- Paxlovid
 - Indicated to treat mild-moderate COVID19 infection initiated within 5 days of symptom onset
 - Dosing: 3 tablets (Nirmatrelvir 300 mg with ritonavir 100 mg) twice daily x 5 days
 - Renal adjustments
 - CrCl 30-59: 2 tablet combination twice daily x 5 days [150 mg nirmatrelvir (1 tab) plus 100 mg ritonavir (1 tab)]
 - CrCl < 30: contraindicated
- Potential for drug-drug interactions with Paxlovid and CNI/mTOR's
 - Ritonavir: very potent CYP3A4 inhibitor
 - Increases levels of CNIs and mTORs significantly
 - Majority of effect (mean 70-80%, 95% CI 10-92%) resolves within 48 hours of last dose.
 - Near complete resolution of effect (mean 95-96%, 95% CI 90-99%) within 7 days of last dose
 - Recommended CNI/mTOR dosing modification while on concomitant Paxlovid are summarized in the table below

Days	Paxlovid	Tacrolimus or mTOR	Cyclosporine
1	Take as prescribed twice daily for 5 days	HOLD therapy (Days 1-7)	Continue therapy at an 80% reduced dose (Days 1-7)
2			
3			
4			
5			
6	n/a		
7	n/a		
8 (48 hrs post Paxlovid)	n/a	Resume therapy at dose on prior to starting Paxlovid (Day 8)	Resume therapy at dose on prior to starting Paxlovid (Day 8)
		- Obtain drug level as soon as possible to evaluate if adjustments warranted (ideally day 7-8 as just restarting therapy) - Must consider patient specific factors such as: time post-transplant, rejection/infection history, other immunosuppression	

- Frequent laboratory monitoring is warranted and should be prescribed even in the setting of COVID19
- Potential for drug-drug interactions with Paxlovid and other (non-immunosuppressant) drugs should also be evaluated prior to initiating therapy
 - Examples of some common drug interactions with Paxlovid include: atorvastatin, clopidogrel, nifedipine, rosuvastatin