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Renal Dosing of Antiviral Agents for COVID-19 (Case)

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Disclosures

- Unrestricted educational and research grants (paid to institution/organization):
  - Abbvie, Gilead, Merck, ViiV
- Speaker honoraria/consulting/advisory board:
  - Gilead, Merck, Pfizer, ViiV

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Case

- 68 yo male, HIV+ 1986, virally suppressed since 2004.
- Comorbidities include hepatitis B, seizure disorder, depression, CKD (eGFR ~27). Resides in assisted living home.
- Medications:
  - Bictegravir/emtricitabine/TAF, levetiracetam 500 mg BID, atorvastatin 10 mg, olanzapine 25 mg, sertraline 25 mg, calcitriol 0.25 ucg, acetaminophen prn

- Oct/2023 →Diagnosed with COVID

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Renal Impairment & COVID-19

- Patients with renal impairment at increased risk for severe outcomes with COVID-19
- COVID-19 can cause renal issues (AKI, tubulopathy, glomerulopathy)

- Need to know how to dose COVID agents in people with renal impairment
  - However, limited PK/safety data in this population
  - Exclusion from clinical trials, monograph restrictions

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COVID Antivirals in Renal Impairment

- Remdesivir
- Molnupiravir
- Nirmatrelvir/ritonavir

- Focus on experience in patients with advanced renal impairment (eGFR<30)

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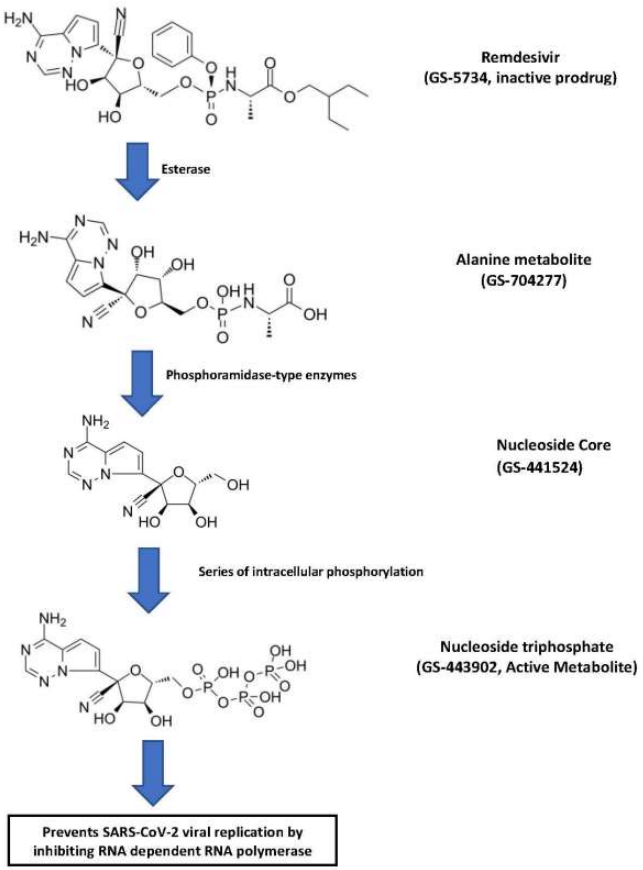
Remdesivir Pharmacokinetics



- Dosing: 200 mg IV day 1, then 100 mg IV daily
  - Mild-moderate: 3 days total
  - Hospitalized: 5 days total, can be extended to 10
- Remdesivir is rapidly converted to nucleoside core (GS-441524), activated intracellularly to TP analogue GS-443902
- GS-441524 primarily undergoes renal clearance

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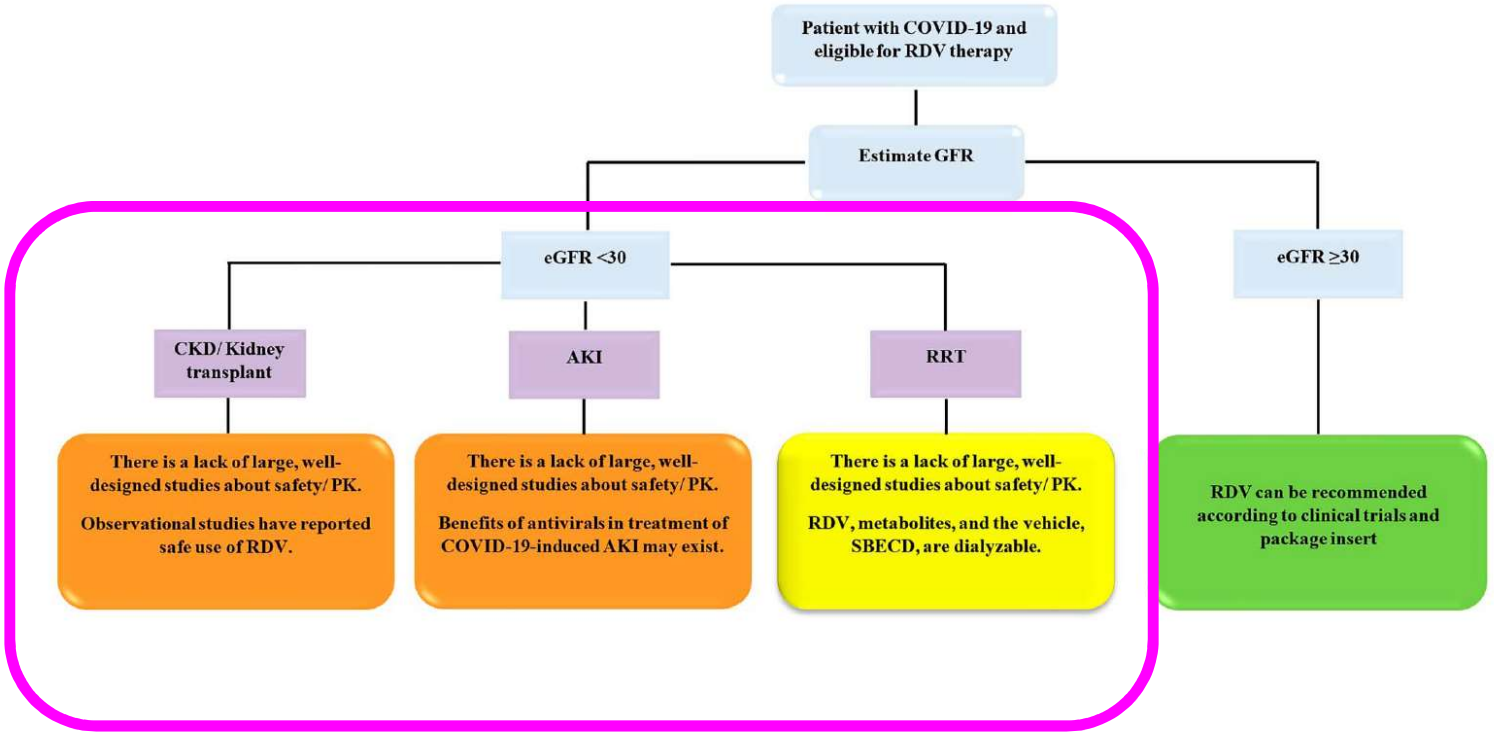
Remdesivir in renal dysfunction



- Not recommended in eGFR<30 (manufacturer)

Davoudi-Monfared et al. American Journal of Therapeutics (2022) 29(5)

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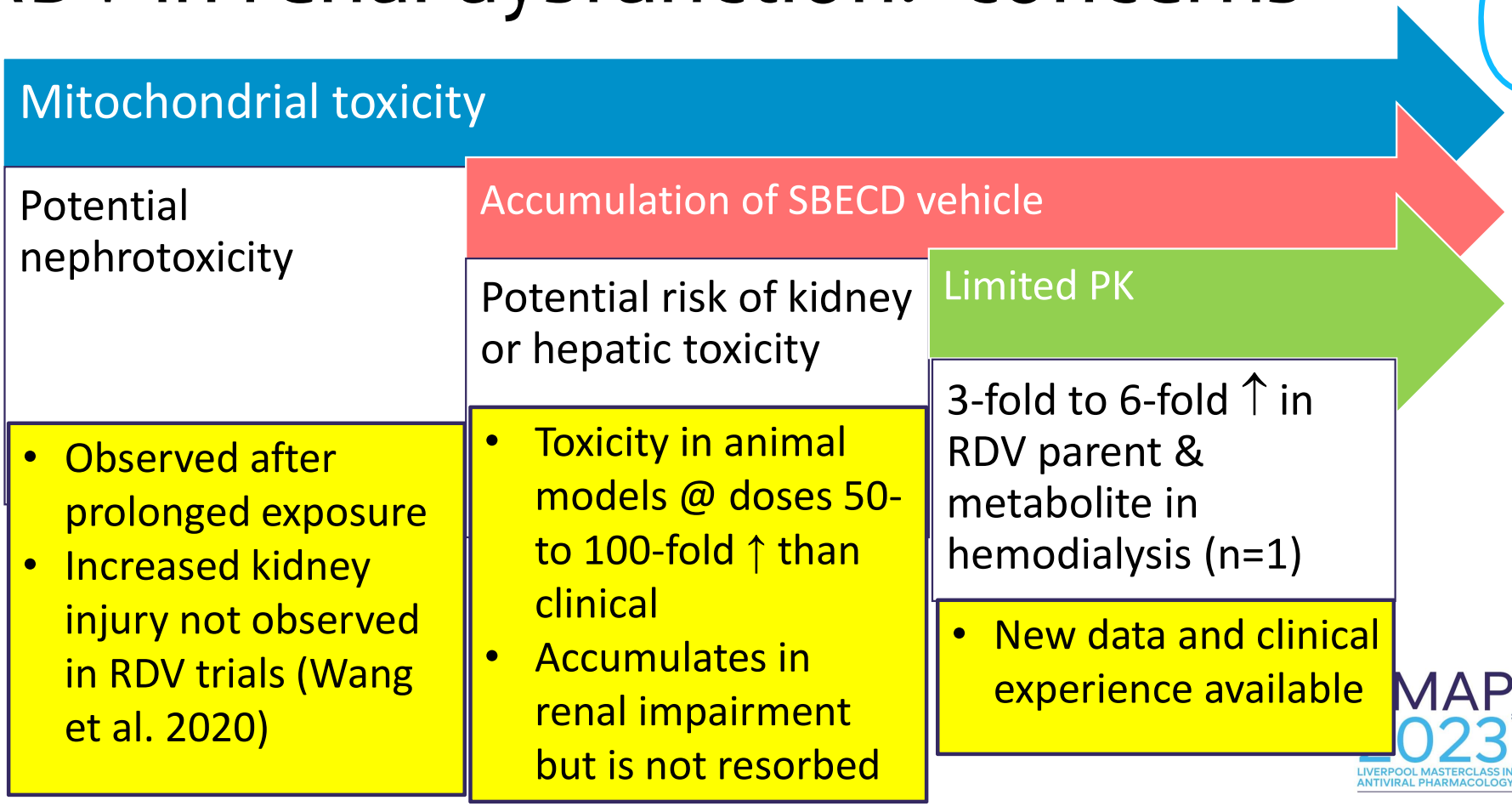
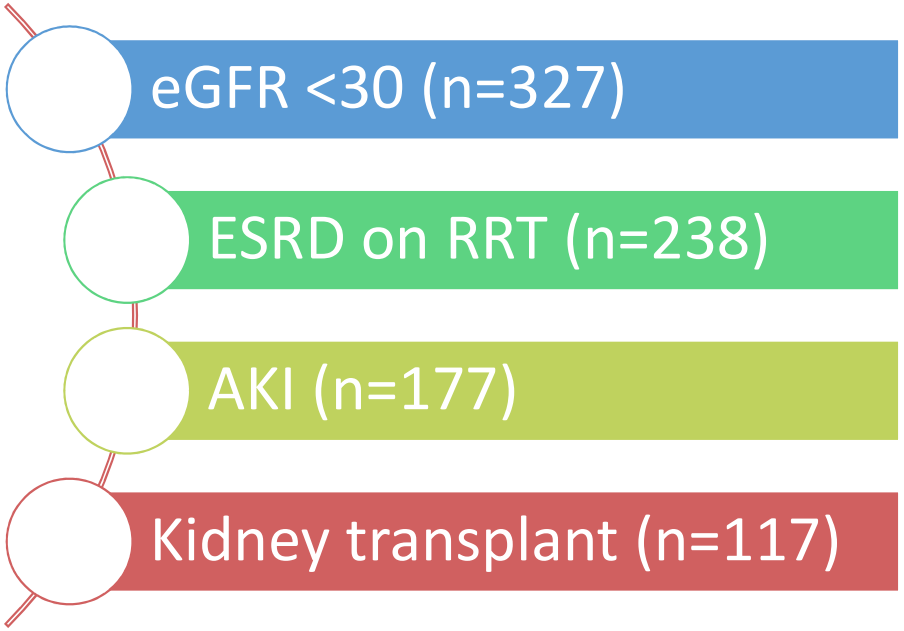
RDV in renal dysfunction: concerns



RDV in COVID-19 patients with renal impairment: systematic review

Eligible studies (n=22) including:
Cohort (n=8)
Observational (n=8)
Case series (n=3)
Case report (n=3)

- No increase in adverse effects (hepatic, renal, GI) attributable to remdesivir vs. patients with normal renal function were reported



Davoudi-Monfared et al. Am J Therap 2022;29:e520-33.

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Review

Remdesivir Use in the Real-World Setting: An Overview of Available Evidence

- Included 4 additional publications of patients with renal impairment vs. previous systematic review
  - Hemodialysis (n=436) Lim et al. 2022; Kikuchi et al. 2021.
  - Kidney transplant (n=165) Elec et al. 2022
  - Advanced kidney disease eGFR<30 (n=444) Stancampiano et al. 2022

- "*All real-world studies showed that remdesivir was relatively safe and well-tolerated in patients with severe renal disease*"

Akinosoglou et al. Viruses 2023;15:1167

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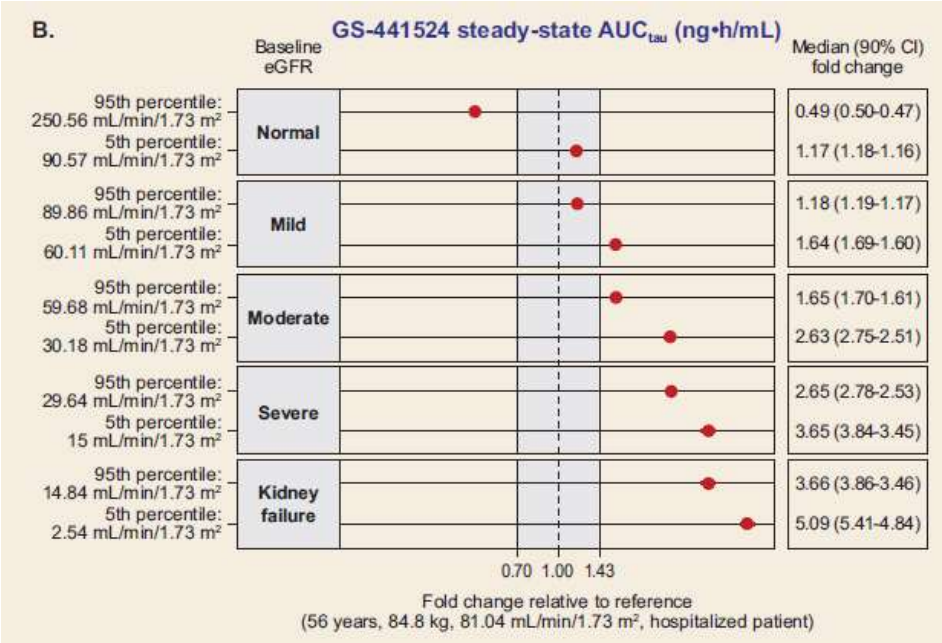
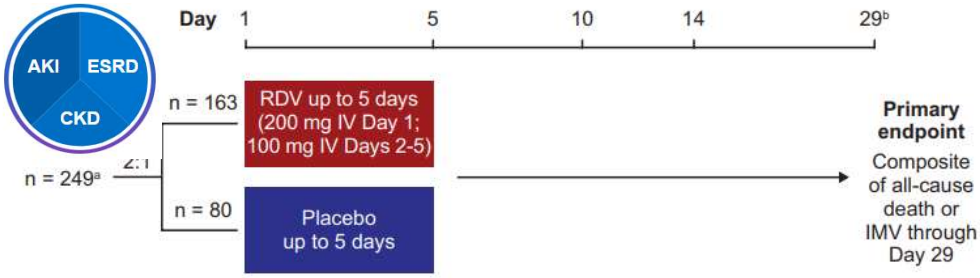
REDPINE: Safety of RDV in hospitalized patients with moderate/severe renal insufficiency

- PopPK modeling:
  - Up to 5-fold ↑ AUC metabolite





RDV, remdesivir; IV, intravenous; IMV, invasive mechanical ventilation.
[a]249 participants were randomised, but 6 were not treated.
[b]If a participant was discharged prior to Day 29, a phone follow-up was completed on Days 29 and 60.

- No significant different in all-cause death or IMV by day 29
- No new safety signals identified with increasing concentrations of the GS-441524 metabolite or the excipient SBECD

Humeniuk et al. CROI 2023, #514. Santos et al. ECCMID 2023, #P2635.

Remdesivir in eGFR<30 mL/min

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	U.S. FOOD & DRUG ADMINISTRATION	Health Canada / Santé Canada
10/2023	07/2023	06/2023
No dose adjustment required	No dose adjustment required	Do not use. Discontinue immediately if eGFR<30

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Remdesivir in eGFR<30 mL/min

JAMA Network Open

Research Letter | Infectious Diseases

Remdesivir in Patients With Severe Kidney Dysfunction
A Secondary Analysis of the CATCO Randomized Trial

Matthew Cheng, MD, CM; Rob Fowler, MDCM, MS(Epi); Srinivas Murthy, MD, CM, MHSc; Ruxandra Pinto, PhD; Nancy L. Sheehan, PharmD, MSc; Alice Tseng, PharmD

Discussion

In patients with eGFR less than 30 mL/min/1.73 m^2 at baseline who received remdesivir, there was no increased risk of transaminitis or toxic kidney effects at day 5.

JAMA Network Open 2022;5(8):e2229236.

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Molnupiravir Pharmacokinetics

- Prodrug of NHC, rapidly converted to NHC-TP
- Minimal renal excretion

- EUA label:
  - Population PK analysis: no impact of mild/moderate RI on PK of NHC
  - PK not evaluated in eGFR<30
  - Severe RI, ESRD, dialysis not expected to have significant impact on NHC pk

- No dose adjustment required in any degree of renal impairment

Lagevrio EUA, October 2023. Yucel HE. Med Sci Discov 2022;6:371-4.

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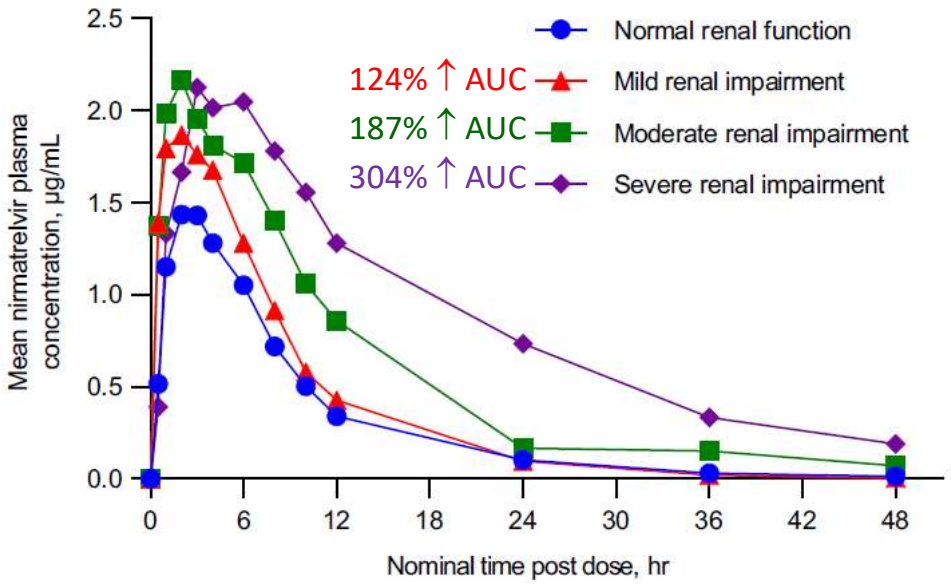
Molnupiravir Safety in Severe Renal Impairment

- Phase III study in outpatients (MOVe-OUT) excluded eGFR<30 or dialysis patients
- Real-world experience:

Study	Stage of CKD	Adverse effects
Dufour et al. (2023)	• N=3 maintenance hemodialysis • N=1 stage 4: transplant (eGFR 18) • N=1 stage 5 (eGFR 11)	• None reported • Renal function remained stable
Cho et al. (2023)	• N=11 stage 4 (eGFR 15-30) • N=1 stage 5 (eGFR <15) • N=1 stage 5D (eGFR<15 on RRT)	• GI upset (n=3), leading to early drug d/c in 2 • 1 patient with schizoaffective disorder hospitalized on day 3 due to worsening insomnia & visual hallucinations

Dufour et al. Kidney Res Clin Pract 2023;42:275-8. Cho et al. Nephrol Dial Transplant 2023;38:1912-4.

Nirmatrelvir is a CYP3A4 substrate but metabolic clearance is minimal when boosted with ritonavir



eGFR mL/min	Recommendation (monograph)
60 to <90 (mild)	Standard dose
30 to <60 (moderate)	↓ to 150/100 mg BID
<30 (severe)	Not recommended

Toussi S et al. CPT 2022;112:892-900. Cdn Paxlovid monograph, 3/10/2023

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NMV/r in dialysis or eGFR<30: data

Standard dosing/adjusted → 50% dose reduction (=moderate RI) → 75% dose reduction

NMV 300/100 BID (Dong Rong 2023)

- N=8 critically ill patients on CCRT; 5 received standard NMVr dose
- >10x higher NMV vs historical

NMV 150 or 300 mg QD with rtv 100 mg BID (Lu 2023)

- n=18 on dialysis: 132-238% ↑ Cmin
- More AEs with higher NMV dose

NMV 150 mg/rtv 100 mg BID

- Lingscheid (2022): PK in hemodialysis (n=4); 4-fold ↑ Cmax but no accumulation
- Real world experience (Wales): n=12, similar side effect profile as in pts with higher eGFR

NMV 300 /100 mg x 1, then 150 mg/rtv 100 mg daily

- Hiremath (2023): n=134 on dialysis. 96% completed treatment; well tolerated, no SAEs
- Chan (2023): n=65 (59 dialysis, 6 eGFR<30): well tolerated, AEs similar as eGFR>30

UKRPG

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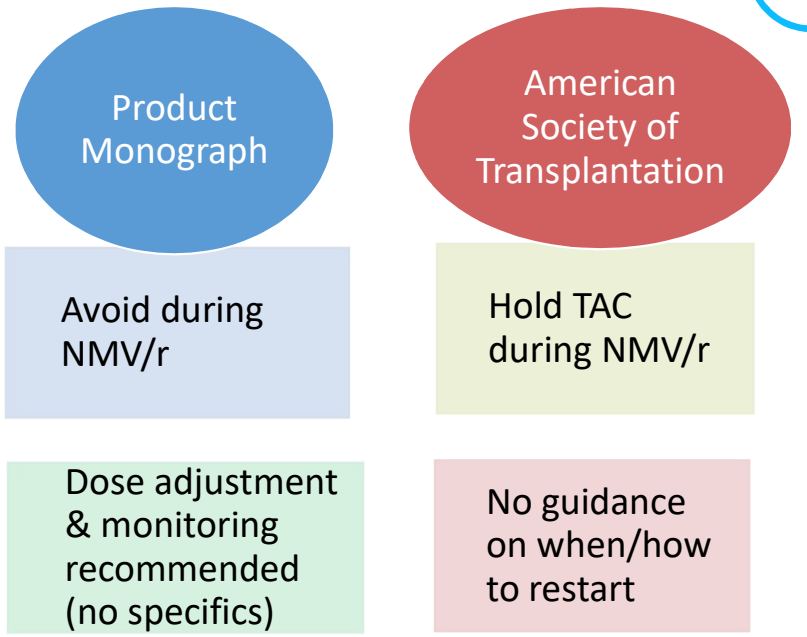
Lingscheid et al. AAC 2022;66:1-4. UKRPG 2023. Lu et al. Front Pharmacol 2023; Hiremath et al. CJASN 2023;18:485-90. Chan et al. CID 2023.

Dosing NMV/r in kidney transplant patients

- Transplant immunosuppressives:
  - Up to 10-fold ↑ in CNI concentrations
- NMV/r + tacrolimus[1]: significantly associated with AKI (41.13%), serum creatinine ↑ (14.18%), renal impairment & renal failure (@2.84%)



1. Qin et al. Exp Opin Drug Safety 2023.

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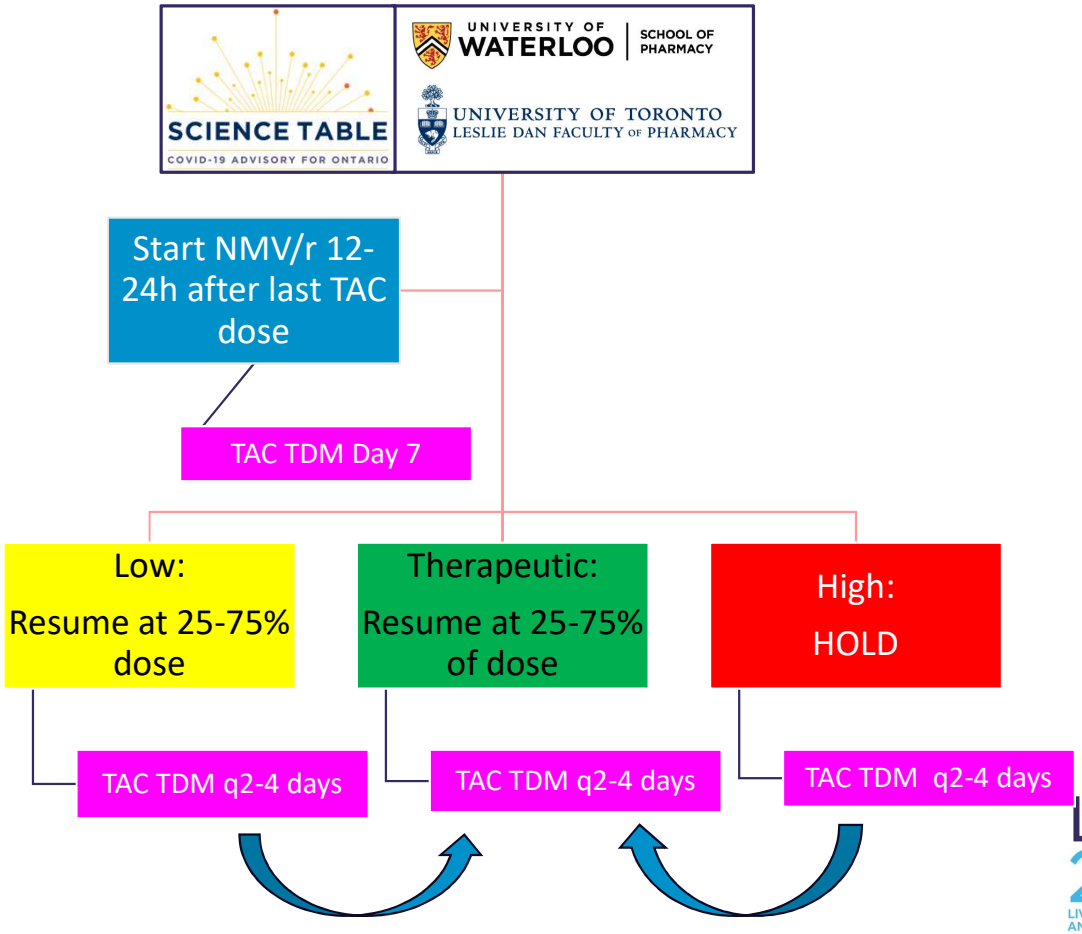
Dosing NMV/r with tacrolimus: initial



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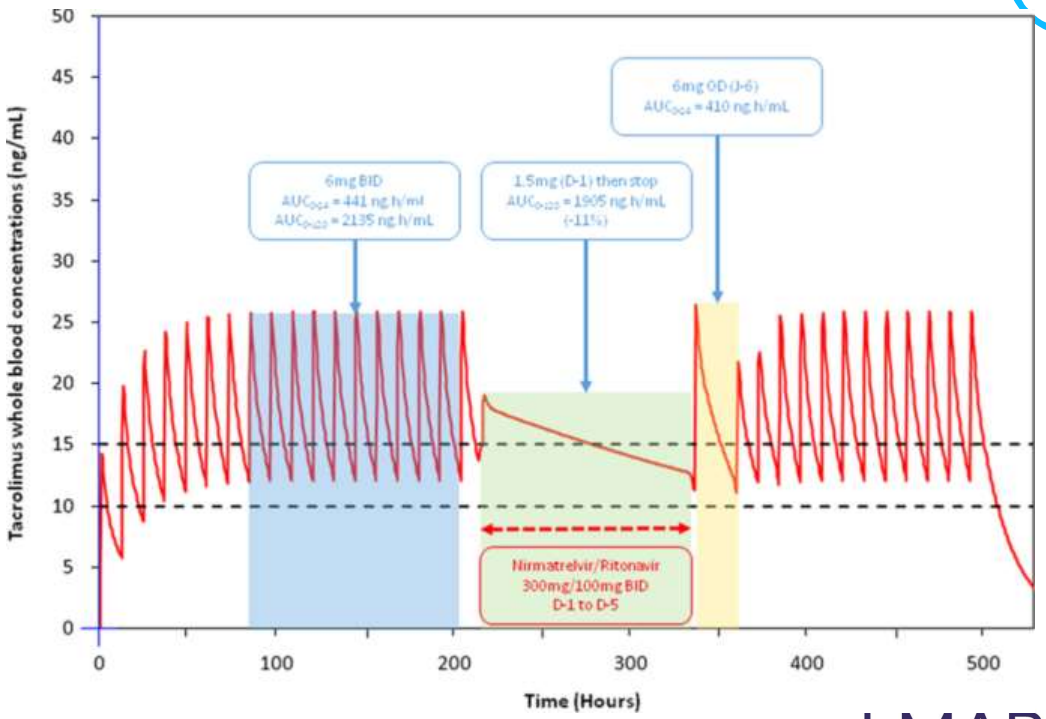
Yes We Can (Use Nirmatrelvir/Ritonavir Even in High Immunological Risk Patients Treated with Immunosuppressive Drugs)!

Proposed algorithm (based on simulation model):

- Day 1 (start of NMV/r): 1/8th TAC dose
- Days 2-5: hold TAC
- End of Day 6: 50% TAC dose
- Day 7: 75% TAC dose
- Day 8: 100% TAC dose



Lemaitre F. Clin Pharmacokinet 2022;61:1071-3.

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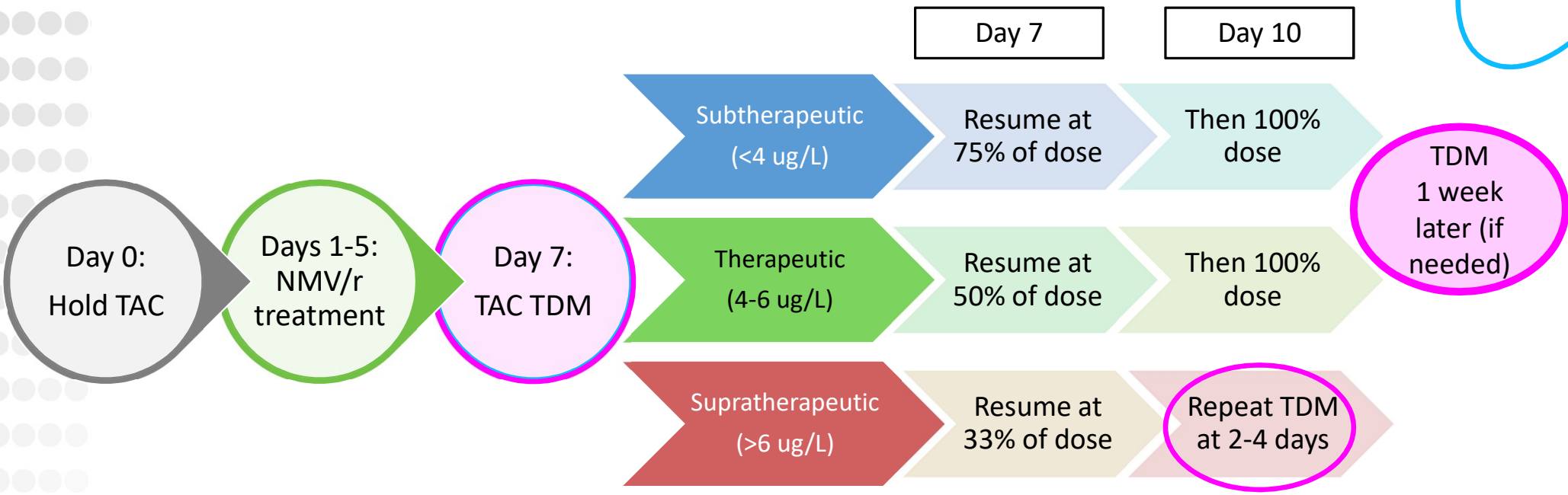
Simplified TAC dosing with NMV/r



- Similar proportion of patients within therapeutic range by 2nd TDM with simplified protocol (n=20) vs standard OST protocol (n=24)
- Low incidence of TAC toxicity, no episodes of acute rejection

Giguere et al. CJASN 2023;18:913-9.

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Case

- 68 yo male, HIV+, hepatitis B, seizure disorder, CKD (eGFR 27), in assisted living home
  - Medications: B/F/TAF, levetiracetam, atorvastatin, olanzapine, sertraline, calcitriol, acetaminophen

- Remdesivir: not logistically feasible

- Molnupiravir: not available in Canada

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Case

- COVID: prescribed NMV/r at modified dose

Special Dosing Considerations:

eGFR† <30 mL/min:
Day 1: Nirmatrelvir 300 mg and ritonavir 100 mg
Days 2-5: Nirmatrelvir 150 mg and ritonavir 100 mg once daily.

- DDIs:
  - Held: atorvastatin
  - Continued other comedications including ARVs

Updated: December 12, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid™*)

What Prescribers and Pharmacists Need to Know

UNIVERSITY OF WATERLOO | SCHOOL OF PHARMACY

UNIVERSITY OF TORONTO LESLIE DAN FACULTY OF PHARMACY

Nirmatrelvir/ritonavir: what prescribers and pharmacists need to know (Dec 12, 2022)

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Summary

- Emerging data support use of COVID antivirals in patients with severe renal impairment

- Remdesivir & molnupiravir:
  - Standard dose in renal impairment
  - Potential access/logistical barriers

- Nirmatrelvir/ritonavir:
  - Dose reduction in eGFR<30
  - Simplified algorithm for dosing with transplant immunosuppressives

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