### Prescribing Nirmatrelvir/Ritonavir (Paxlovid) for COVID-19 in Advanced Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Clinical Journal of the American Society of Nephrology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>CJASN-0527-05-22.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Invited Features</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>25-May-2022</td>
</tr>
</tbody>
</table>
| Complete List of Authors: | Hiremath, Swapnil; University of Ottawa, Division of Nephrology, Department of Medicine  
McGuinty, Michaeline; University of Ottawa, Division of Infectious Disease, Department of Medicine  
Argyropoulos, Christos; University of New Mexico Health Sciences Center, Division of Nephrology  
Brimble, K. Scott; McMaster University, Division of Nephrology, Department of Medicine  
Brown, Pierre; University of Ottawa, Division of Nephrology, Department of Medicine  
Chagla, Zain; McMaster University, Division of Infectious Disease, Department of Medicine  
Cooper, Rebecca; Ontario Health, Ontario Renal Network; Trillium Gift of Life Network  
Hoar, Stephanie; University of Ottawa, Division of Nephrology, Department of Medicine  
Juurlink, David; Sunnybrook Hospital, Department of Medicine; University Health Network  
Treleavan, Darin; McMaster University, Division of Nephrology, Department of Medicine; Trillium Gift of Life Network  
Walsh, Michael; McMaster University, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence and Impact; Population Health Research Institute  
Yeung, Angie; Ontario Health, Ontario Renal Network  
Blake, Peter; Western University, Division of Nephrology, Department of Medicine; Ontario Health, Ontario Renal Network |
| Keywords: | COVID-19, dialysis, drug metabolism, pharmacokinetics, transplantation, chronic kidney disease |
Prescribing Nirmatrelvir/Ritonavir (Paxlovid) for COVID-19 in Advanced Chronic Kidney Disease

Swapnil Hiremath, Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Canada
Michaeline McGuinty, Division of Infectious Disease, Department of Medicine, University of Ottawa, Ottawa, Canada
Christos Argyropopulos, Division of Nephrology, Albuquerque, New Mexico
K. Scott Brimble, Division of Nephrology, Department of Medicine, McMaster University, Hamilton, Canada; Ontario Renal Network, Ontario Health, Toronto, Canada
Pierre Antoine Brown, Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Canada
Zain Chagla, Division of Infectious Disease, Department of Medicine, McMaster University, Hamilton, Canada
Rebecca Cooper, Ontario Renal Network and Trillium Gift of Life Network, Ontario Health, Toronto, Ontario
Stephanie Hoar, Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Canada
David Juurlink, Department of Medicine, Sunnybrook Hospital and University Health Network, Toronto, Canada
Darin Treleaven, Division of Nephrology, Department of Medicine, McMaster University, Hamilton, Canada; Ontario Health, Trillium Gift of Life Network, Toronto, Canada
Michael Walsh, Department of Medicine, McMaster University, Hamilton, Canada
Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada
Population Health Research Institute, Hamilton Health Sciences / McMaster University, Hamilton, Canada
Angie Yeung, Ontario Renal Network, Ontario Health, Toronto, Ontario
Peter Blake, Division of Nephrology, Department of Medicine, Western University, London, Canada;
Ontario Renal Network, Ontario Health, Toronto, Canada

Address for Correspondence
Swapnil Hiremath
1967 Riverside Drive
Ottawa, ON
Canada; K1H7W9
email: shiremath@toh.ca Fax: +1 613 7388337
Introduction

As of Dec 2021, 18.2 million have died globally from Coronavirus disease (COVID-19) due to the Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2) and millions more suffer from longer term consequences (1). Morbidity and mortality from COVID-19 is higher in immunocompromised patients including those with advanced chronic kidney disease (CKD) (stages 4 and 5) and those with kidney failure. Even after propensity-score matching for the higher comorbid disease burden, a higher risk for hospitalization (risk ratio [RR] 1.6, 95% confidence interval [CI] 1.3 – 1.9) and mortality (RR 1.3 95% CI 1.3 to 2.0) in severe CKD was reported (2). While case fatality rates for patients on dialysis have fallen in recent waves and with vaccination, they remain markedly higher than those in the general population (3).

Though vaccines for COVID-19, particularly the mRNA vaccines, have reduced the severity and transmissibility of COVID-19, their effectiveness is attenuated in dialysis and transplant populations. Estimates of early antibody response in dialysis patients were 89% relative to healthy controls, conferring incomplete protection which wanes over time (4). For kidney transplant recipients, antibody response was only 35% with small increments to repeat vaccination (4, 5). For newer variants (such as Omicron), higher antibody titers are required for viral neutralization and vaccination alone will not provide sufficient protection against infection and severe outcomes in dialysis and transplant patients (6).

Patients with advanced CKD, patients receiving dialysis, and kidney transplant recipients are frequently excluded from clinical trials evaluating new drugs. This phenomenon, coined ‘renalism’, recurred with COVID-19. A review of trial registries reported that 218 of 484 COVID-19 trials (45%) excluded patients with CKD (7). Studies evaluating nirmatrelvir/ritonavir (Paxlovid, Pfizer Inc.), have similarly excluded patients with advanced CKD despite their relevance to this population. Nirmatrelvir/ritonavir however has pharmacology and toxicity data that can provide a basis for its use in advanced CKD (8).

Nirmatrelvir/Ritonavir Efficacy

Nirmatrelvir is an orally administered antiviral agent inhibiting the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme (Mpro) also referred to as 3C-like protease (3CLpro) or nsp5 protease which renders the protein incapable of processing polyprotein precursors and prevents viral replication. The EPIC-HR trial (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) evaluated the safety and efficacy of nirmatrelvir plus ritonavir in non-hospitalized adults with mild-to-moderate COVID-19 at high risk for progression to severe disease (9). Nirmatrelvir/ritonavir was initiated at a dose of 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days within 5 days of symptom onset. The incidence of COVID-19-related hospitalization or death by day 28 was 89.1% lower in the nirmatrelvir group than in the placebo group. There were 13 deaths, all in the placebo group. On this basis, nirmatrelvir/ritonavir is indicated for the treatment of mild-to-moderate COVID-19 (i.e. for outpatient treatment) in adults with positive SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Patients with advanced CKD are at such high risk, but were excluded from this trial, and there are theoretical concerns about drug accumulation and
safety in these patients. For these reasons, the product monograph states that it is ‘not recommended’
for those with eGFR (estimated glomerular filtration rate) < 30.

**Pharmacology of Nirmatrelvir/Ritonavir**

Nirmatrelvir is co-administered with a low dose (100 mg) of ritonavir which acts as a pharmacokinetic enhancer. Ritonavir is a CYP3A4 inhibitor and enhances nirmatrelvir’s bioavailability, allowing required therapeutic concentrations to be achieved. In preclinical studies the concentration threshold that correlated with efficacy was 181nM (292 ng/mL) (8). Hence, the desired dose of nirmatrelvir is that which maintains a trough level above this, and led to the 300 mg dose chosen in the EPIC-HR trial. Nirmatrelvir has a molecular weight of 499.5 Da, is ~35% renally excreted and is 70% protein bound. Ritonavir is mostly hepatically metabolized and is 99% protein bound. Thus nirmatrelvir is expected to accumulate with decreasing kidney function. In a phase 2 study (C4671005) of 8 patients with serious kidney impairment (eGFR < 30 ml/min/1.73 m$^2$, not on dialysis) the mean concentration at 24 hours was 694.2 ng/mL after a single dose of 100 mg nirmatrelvir (>2 times the required 292 ng/mL).

**Adverse Effects of Nirmatrelvir/Ritonavir**

From animal data, no adverse effects were observed at 1000 mg/kg/day, which correspond to an exposure ~ 8 times higher than the recommended human dose (8). Nirmatrelvir-related adverse events following repeated dosing in monkeys at up to 600 mg/kg/day were limited to emesis, increased fibrinogen, and increased transaminases, which completely reversed within 2 weeks. In the EPIC-HR trial, serious adverse events were lower with nirmatrelvir/ritonavir (1.6%) compared to placebo (6.6%) (9). Adverse events reported by more than 1% of the participants were dysgeusia, nausea, vomiting, headache, diarrhea, and fever. In the phase 2 study with eGFR < 30 ml/min/1.73 m$^2$, 2/8 (25%) reported dysgeusia and dry mouth compared to none in the other arms with higher kidney function (8). Overall, nirmatrelvir/ritonavir has a favorable safety profile, with no evidence of dose-dependent toxicity.

**Rationale for Dosing in CKD and Dialysis Patients**

A single dose of nirmatrelvir 100 mg inhibited Mpro enzymatic activity at 24 hours in patients with eGFR < 30 ml/min/1.73 m$^2$. Hemodialysis will clear a clinically insignificant amount of nirmatrelvir, based on what is known about its molecular size, protein binding, and volume of distribution. The safety profile of nirmatrelvir is favorable, with few serious adverse effects, and the animal data are not indicative of dose dependent toxicity. Nirmatrelvir is currently formulated as a 150 mg tablet and dosed at 300 mg with 100 mg ritonavir twice a day for patients with normal kidney function, and at 150 mg with 100 mg ritonavir twice a day in those with eGFR 30-60. A dose of 300 mg nirmatrelvir (with 100 mg ritonavir) on day 1, followed by 150 mg nirmatrelvir (with 100 mg ritonavir) administered daily, given after hemodialysis on dialysis days, should provide effective blood concentrations for enzyme inhibition (see Box 1). Minimal drug accumulation is expected based on the short duration of therapy and single dose pharmacokinetics. A lower dose of 150 mg every 48 hours could be considered for patients weighing less than 40 kgs.
Drug interactions are important since ritonavir is a potent CYP3A4 inhibitor, and an inducer of other cytochrome p450 enzymes. Commonly used drugs in patients with CKD with important drug interactions include statins, calcium channel blockers, and direct acting oral anticoagulants (see Box 1). These interactions are not always a contraindication to therapy and are mitigated by temporarily suspending or reducing the doses of CYP3A4 metabolized drugs. Support from pharmacists may help identify appropriate, temporary changes in treatments.

A small case series using this modified lower dose of nirmatrelvir/ritonavir in 15 dialysis patients with COVID-19 reported rapid symptom resolution, with no safety signal, and highlighted the need to review drug interactions which were common in this population (10).

Rationale for Dosing in Kidney Transplant Recipients
In patients with a kidney transplant, drug-drug interactions are an additional concern. The inhibition of drug metabolism due to ritonavir can result in extremely toxic levels (10-fold higher) of calcineurin inhibitors (CNIs), and prolonged half-life. To a lesser extent, levels of mycophenolic acid and sirolimus may also be affected. Even with eGFR > 30, CNIs must be held or decreased, and close monitoring of CNI levels is required after therapy is complete to also avoid low CNI levels. The American Society of Transplantation also provided guidance on use of nirmatrelvir/ritonavir in kidney transplant recipients with eGFR > 30 (see https://www.myast.org/sites/default/files/AST%20Statement%20on%20Oral%20Antiviral%20Therapy%20for%20COVID%20Jan%202020%20282%29.pdf). Use in patients with eGFR < 30 should be considered cautiously in consultation with experienced teams, including infectious disease and pharmacy. Though not discussed separately here, similar considerations should also apply to patients with CKD due to glomerulonephritis receiving these immunosuppressive drugs.

Conclusion
The use of nirmatrelvir/ritonavir has been shown to be particularly effective in disarming the COVID-19 virus, especially in high-risk populations. Despite a relative dearth of data for the use and dosing of nirmatrelvir/ritonavir in patients with advanced CKD and those with a kidney transplant, these patients are at particularly high risk for COVID-19 morbidity and mortality and should not be excluded from therapy simply because of lack of data. We suggest patients with advanced CKD (eGFR < 30 ml/min/1.73 m²) and those receiving dialysis who contract COVID-19 be offered the low dose nirmatrelvir/ritonavir regimens. This should be preceded by a discussion between the prescribing physician and the patient about the potential risks and benefits of the treatment including alternative therapies. Special care must be taken with patients receiving immunosuppressive therapies, especially those with a kidney transplant, as drug-drug interactions can seriously affect the half-lives of commonly used anti-rejection strategies.
Disclosures

C. Argyropoulos reports consultancy agreements with Baxter, Bayer, Otsuka, and Quanta; research funding from Akebia and Alkahest; and serving in an advisory or leadership role for Baxter Healthcare, Bayer, Health Services Advisory Group, and Quanta.

P. Blake reports honoraria from Baxter Global, serving on the editorial board of *American Journal of Nephrology*, and serving as Medical Director of Ontario Renal Network - this is a paid role.

K.S. Brimble reports serving as Provincial Lead of Ontario Renal Network.

P.A. Brown reports consultancy agreements with Amgen Canada, AstraZeneca Canada, and Otsuka Canada; research funding from Otsuka Canada; and honoraria from AstraZeneca Canada and Otsuka Canada.

Z. Chagla reports consultancy agreements with Pfizer, research funding from Gilead and Roche, and speakers bureau for Gilead and Pfizer.

S. Hiremath reports serving on the editorial boards of *American Journal of Hypertension*, *American Journal of Kidney Disease*, and *Canadian Journal of Cardiology* and on the Board of Directors for NephJC (not for profit educational entity).

D. Juurlink has received payment for lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids. He is a member of Physicians for Responsible Opioid Prescribing, a volunteer organization that seeks to reduce opioid-related harm through more cautious prescribing practices.

M. Mcguinty reports research funding from VBI.

M. Walsh reports employment with Ontario Renal Network; research funding from British Heart Foundation, Canadian Institutes of Health Research, Health Research Council, National Health and Medical Research Council, National Institute of Health Research, and Vifor (no salary support received through any research funding); serving in an advisory or leadership role for Bayer (steering committee, payment to institution) and Otsuka (national leader, payment to institution); and other interests or relationships with Novo Nordisc (event adjudication, payment to institution).

The remaining authors have nothing to disclose.

Funding

None.

Acknowledgments

SH receives research salary support from the Department of Medicine, University of Ottawa.
Author Contributions

Christos Argyropoulos: Writing – review & editing

Peter Blake: Conceptualization, Writing – original draft, Writing – review & editing

K. Scott Brimble: Writing – review & editing

Pierre A. Brown: Writing – original draft, Writing – review & editing

Zain Chagla: Writing – review & editing

Rebecca Cooper: Conceptualization, Writing – review & editing

Swapnil Hiremath: Conceptualization, Supervision, Writing – original draft, Writing – review & editing

Stephanie Hoar: Conceptualization, Writing – review & editing

David Juurlink: Writing – original draft, Writing – review & editing

Michaeline McGuinty: Conceptualization, Writing – original draft, Writing – review & editing

Darin Treleaven: Conceptualization, Writing – review & editing

Michael Walsh: Conceptualization, Writing – review & editing

Angie Yeung: Writing – review & editing
Box 1. Dosing Guidance For Nirmatrelvir/Ritonavir In Advanced Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Unvaccinated or vaccinated CKD, dialysis, transplant recipients in the outpatient setting, with COVID-19 Presence of symptoms, with therapy initiation possible within 5 days of symptom onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in CKD, eGFR &lt;30, not on dialysis</td>
<td>300 mg nirmatrelvir + 100 mg ritonavir both on day 1 Then 150 mg nirmatrelvir + 100 mg ritonavir once a day for 4 more days</td>
</tr>
<tr>
<td>Dose in dialysis</td>
<td>300 mg nirmatrelvir + 100 mg ritonavir both on day 1 Then 150 mg nirmatrelvir + 100 mg ritonavir once a day for 4 more days, to be dosed after dialysis*</td>
</tr>
<tr>
<td>Important drug interactions*</td>
<td>Direct-acting oral anticoagulants (DOACs), warfarin, statins, calcium channel blockers (CCBs), alpha-adrenergic antagonists, hydromorphone, trazodone, calcineurin inhibitors, and anticonvulsants Pharmacist review advised</td>
</tr>
<tr>
<td>Transplant considerations</td>
<td>Hold or decrease calcineurin inhibitors for duration of nirmatrelvir/ritonavir therapy Restart at 48 to 72 hours post course completion at a lower dose Monitor drug levels closely to guide further adjustment</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Adverse events reported by more than 1% of the participants were dysgeusia, nausea, vomiting, headache, diarrhea, and fever. No dose dependent toxicity reported Specific adverse effects in CKD population are not yet known</td>
</tr>
<tr>
<td>Further considerations</td>
<td>The actual efficacy of nirmatrelvir/ritonavir in CKD, and the interaction with vaccination status and emerging variants, is yet unknown These dosing suggestions are based on pharmacology and should be reviewed once more data become available A discussion between the prescribing physician and the patient about the potential risks and benefits of the treatment, including alternative therapies, is essential prior to starting nirmatrelvir/ritonavir in advanced CKD</td>
</tr>
</tbody>
</table>

* The dose should be reduced to 150 mg nirmatrelvir + 100 mg ritonavir on day 1 then 150 mg nirmatrelvir + 100 mg ritonavir every 48 hours for 2 more doses, to be given after dialysis if patient weight is less than 40 kg.

* This list is not exhaustive and complete. Some agents (e.g., statins, in particular atorvastatin, simvastatin, lovastatin) could be held for the 5 days, while others (e.g., DOACs or CCBs) could be held or dose reduced in half as clinically appropriate; for others (hydromorphone), the analgesic effect may be reduced due to less conversion to active form of drug. See https://www.covid-19-druginteractions.org/checker for more details.
References


8. FDA. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID. US FDA; 2021 [cited 2022 05/02]; Available from: https://www.fda.gov/media/155050/download.
