Therapeutic drug monitoring and dosage adjustments of immunosuppressive drugs when combined with nirmatrelvir/ritonavir in patients with COVID-19

Florian Lemaitre, Klemens Budde, Teun van Gelder, Stein Bergan, Roland Lawson, Ofelia Noceti, Raman Venkataramanan, Laure Elens, Dirk Jan a R Moes, Dennis A Hesselink, et al.

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1 **Therapeutic drug monitoring and dosage adjustments of immunosuppressive drugs when**
2 **combined with nirmatrelvir/ritonavir in patients with COVID-19**

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4 **Florian Lemaitre, PharmD, PhD**, 1, 2; Klemens Budde, MD 3; Teun Van Gelder, MD, PhD 4; Stein
5 Bergan, PhD 5; Roland Lawson, PharmD, PhD 6; Ofelia Noceti, PharmD, PhD 7; Raman
6 Venkataramanan, PhD 8; Laure Elens, PhD 9; Dirk Jan A.R. Moes, PharmD , PhD 4; Dennis A.
7 Hesselink, MD, PhD 10; Tomasz Pawinski, PharmD, PhD 11; Kamisha L. Johnson-Davis, PhD 12;
8 Brenda C.M. De Winter, PharmD, PhD 13; Smita Pattanaik, MD, DM 14; Mercè Brunet, PhD 15;
9 Satohiro Masuda, PhD 16 and Loralie J. Langman, PhD 17.

10

1	Univ Rennes, CHU Rennes, Inserm, EHESP, IRSET – UMR S 1085, Rennes, France
2	INSERM, Centre d'Investigation Clinique 1414, F-35000 Rennes, France
3	Department of Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany
4	Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, The Netherlands.
5	Department of Pharmacology, Oslo University Hospital and Department of Pharmacy, University of Oslo, Norway.
6	University of Limoges, Inserm U1248, Pharmacology & Transplantation, F-87000, Limoges, France.
7	National Center for Liver Transplantation and Liver Diseases, Army Forces Hospital, Montevideo, Uruguay
8	Department of Pharmaceutical Sciences, School of Pharmacy and Department of Pathology, Starzl Transplantation Institute, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA
9	Integrated Pharmacometrics, pharmacogenetic and pharmacokinetics research group (PMGK) Louvain Drug for Research institute (LDRI), catholic University of Louvain (UCLouvain), Brussels, Belgium
4	Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, The Netherlands.
10	Erasmus MC Transplant Institute, University Medical Center, Rotterdam, The Netherlands
11	Department of Drug Chemistry, Faculty of Pharmacy, Medical University of Warsaw, Warsaw, Poland
12	University of Utah Health Sciences Center and ARUP Laboratories, Salt Lake City, UT, USA
13	Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands.
14	Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh, INDIA
15	Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, CIBERehd, Spain
16	Department of Clinical Pharmaceutics, Faculty of Pharmaceutical Sciences, Himeji Dokkyo University, Japan
17	Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

11

12 **Corresponding Author address:**
13   Florian Lemaitre, PharmD, PhD, Department of Pharmacology, Rennes University Hospital, 2
14 rue Henri Le Guilloux, 35033, Rennes, France. Tel: 0033 223234713. Fax: 0033 299284184. Mail:
15 florian.lemaitre@chu-rennes.fr

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41   Nirmatrelvir/ritonavir (Paxlovid®) consists of a peptidomimetic inhibitor of the SARS-CoV-2 main
42   protease (Nirmatrelvir) and a pharmacokinetic enhancer (Ritonavir). It is approved for the treatment
43   of mild-to-moderate COVID-19. This combination of nirmatrelvir and ritonavir can mediate significant
44   and complex drug-drug interactions, primarily due to the ritonavir component. Indeed, ritonavir
45   inhibits the metabolism of nirmatrelvir through cytochrome P450 3A (CYP3A) leading to higher plasma
46   concentrations and a longer half-life of nirmatrelvir. Co-administration of nirmatrelvir/ritonavir with
47   immunosuppressant drugs is particularly challenging given the major involvement of CYP3A in the
48   metabolism of most of these drugs and their narrow therapeutic range. Immunosuppressant drug
49   exposure will be drastically increased through the potent ritonavir-mediated inhibition of CYP3A
50   resulting in increased risk of adverse drug reactions. While a decrease in immunosuppressive drug
51   dosage can prevent toxicity, an inappropriate dosage regimen may also result in insufficient exposure
52   and a risk of rejection. Here we provide some general recommendations for therapeutic drug
53   monitoring of immunosuppressive drugs and dosing recommendations when co-administered with
54   nirmatrelvir/ritonavir. Particularly, tacrolimus should be discontinued or patients should be given a
55   microdose on day-1 while cyclosporine dosage should be reduced to 20% of the initial dosage during
56   the antiviral treatment. m-TOR inhibitors dosages should also be adapted while mycophenolic acid
57   and corticosteroids are expected to be less impacted.

58

59   **Keywords:** Drug-drug interactions; Transplantation; Calcineurin inhibitors, mTOR inhibitors;
60   Tacrolimus

61

1. Introduction

Paxlovid® is a new solid oral formulation indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who test positive for direct SARS-CoV-2 virus, and who are at high risk for progression to severe COVID-19 [1-4]. Paxlovid® is supplied as 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all the three tablets taken together orally with or without food twice daily for 5 days [1].. No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 L/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of Paxlovid® is modified to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. However, in patients with severe renal impairment or severe hepatic impairment, the use of the nirmatrelvir/ritonavir is not recommended due to limited availability of safety and efficacy data [1, 2].

1.1 Pharmacodynamics:

Nirmatrelvir's chemical name is (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2- oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide] (Figure 1) and is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication [1, 2]. Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 infection in primary human lung alveolar epithelial cell line (EC50 value of 61.8 nM and EC90 value of 181 nM) after 3 days of drug exposure [5]. It was shown to have efficacy against the Alpha (B.1.1.7), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529) SARS-CoV-2 variants [5].

1.2 Pharmacokinetics:

After oral administration of a single dose of nirmatrelvir/ritonavir 300 mg/100 mg, the median time to peak concentration (tmax) of nirmatrelvir was 3 hours (range 1 to 6 h), indicating a relatively rapid absorption. The observed geometric mean (CV%) concentration maximum (Cmax) and the area under the plasma concentration versus time curve from zero to infinity (AUCinf) for nirmatrelvir were 2.21 mg/L (33 %CV) and 23.01 μg*h/mL (23 %CV), respectively [1, 5]. Studies have shown that nirmatrelvir was moderately bound to plasma proteins (69%) and has a mean apparent volume of distribution (Vz/F) of 104.7 L when administered with ritonavir (300 mg nirmatrelvir/100 mg ritonavir) [1].

Based on *in vitro* studies, CYP3A4 is the major contributor (99%) to the oxidative metabolism of nirmatrelvir. However, nirmatrelvir undergoes minimal metabolism when coadministered with ritonavir resulting in high and persisting plasma concentrations [1, 5]. When the protease inhibitor metabolism is inhibited by ritonavir, renal elimination become the major route of nirmatrelvir.[1, 5].

4

In healthy volunteers after single or multiple oral doses of nirmatrelvir/ritonavir as oral suspension the half-life ranged from 6.8 to 9.5 h thereby supporting a twice daily dosing administration regimen [1, 5].

1.3 Clinical trials:

The first-in-human clinical trial of nirmatrelvir started on September 9th, 2020 and was a phase 1B, placebo-controlled single and multiple intravenous ascending dose (SAD and MAD) study evaluating the safety, tolerability, and pharmacokinetics in COVID-19 patients [6][1]. Its efficacy was studied in a pre-omicron variant era phase 2-3 double-blind, randomized, controlled trial in adult patients with a laboratory confirmed diagnosis who were symptomatic, unvaccinated, non-hospitalized and at high risk for progression to severe COVID-19. A total of 2246 adults were randomised to receive either 300 mg of nirmatrelvir along with 100 mg of ritonavir or placebo orally every 12 hours for 5 days [3]. The treatment arm demonstrated a COVID-19–related hospitalization rate of 0.77% (3/389) at 28-days compared to the placebo arm at 7.01%. (27/385). This led to an absolute risk reduction of 6.32% (95% confidence interval [CI], −9.04 to −3.59; P<0.001) and a relative risk reduction of 87.8%. Additionally, the COVID-19–related mortality through day 28 was 0% (0/389) in the treatment group compared to 1.2% (7/385) in the placebo group [3]. Patients treated with nirmatrelvir and ritonavir had a decrease in SARS-CoV-2 viral load by a factor of ten relative to the placebo at day-5 [3]. Due to the satisfactory demonstration of efficacy and safety, Paxlovid® received the Emergency Use Authorisation (EUA) from the US-FDA in December 2021 and conditional marketing authorization by the EMA in January 2022 as the first oral antiviral drug for treating COVID-19 in the outpatient setting [8]. Of note, less than 1% of patients included in the trial were immunocompromised.

1.4 Warnings and Toxicity:

Use of Paxlovid has been associated with potential complications. Dysgeusia, diarrhea, hypertension, and myalgia are the main adverse drug reactions reported in the phase III randomized clinical trial [2, 4, 5].

The combination of nirmatrelvir/ritonavir has significant and complex drug-drug interactions, primarily due to ritonavir. A careful review of the patient's concomitant medications, including over-the-counter medications, herbal supplements, and recreational drugs should be performed to minimize the occurrence of any potential drug-drug interactions (DDI) before prescribing nirmatrelvir/ritonavir [2, 4, 5]. It is suggested that drug interaction potential be comprehensively checked. As an example, French recommendations on managing DDI with nirmatrelvir/ritonavir have been published [9] and the website of the University of Liverpool also provides free access to drug interaction charts [10]. The nature of the drug-drug interactions will be discussed in subsequent sections of this publication.

5

140 Paxlovid is contraindicated with drugs that are potent CYP3A inducers where significantly reduced
141 nirmatrelvir or ritonavir plasma concentrations may lead to potential loss of response to SARS-CoV-2
142 and possible development of resistance.

143

144 On the other hand, ritonavir is a strong inhibitor of cytochrome CYP3A4 and therefore the use of
145 Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for
146 which elevated concentrations are associated with serious and/or life-threatening reactions [2, 4, 5].
147 Moreover, nirmatrelvir/ritonavir could also exhibit potential life-threatening interactions in
148 individuals on immunosuppressive drug (ISD) therapy; which are mainly metabolized by CYP3A4 [2,
149 4, 5].

150

151 Concomitant drug therapy of nirmatrelvir/ritonavir with ISD requires specific consideration to avoid
152 elevated ISD concentrations in the toxic range; in this scenario therapeutic drug monitoring can be
153 beneficial to adjust ISD dosing. This will be the focus of the second part of this publication.

154

155 **2.   Drug-drug interaction with ritonavir-boosted nirmatrelvir**

156 Nirmatrelvir does not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in
157 vitro test, and it does not induce any CYPs at clinically relevant concentrations. However,
158 nirmatrelvir has the potential to irreversibly and time-dependently inhibit CYP3A4 and P-
159 glycoprotein 1 (permeability glycoprotein, P-gp) also known as multidrug resistance protein 1
160 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243
161 (CD243)[1]. While drug-drug interaction between nirmatrelvir and ritonavir is beneficial in the use of
162 Paxlovid®; the potent inhibition of 3A4 by ritonavir can lead to other significant drug interactions.
163 The significant drug-drug interactions in the combination product are primarily due to ritonavir.

164

165 Ritonavir is a substrate of CYP3A and to a lesser extent CYP2D6 and is transported by P-gp [11, 12].
166 Ritonavir is an inducer of CYP1A2, CYP2C9, CYP2C19, CYP2B6 and UGT1A1. It is a potent inhibitor of
167 CYP3A and to a lesser extent of CYP2D6, CYP2C8. Ritonavir displays a paradoxical dose and time-
168 dependent inhibitory/induction effect on CYP3A and on the multidrug efflux transporter P-gp [11].
169 Some of the specific interactions are discussed below.

170 Of note, inflammation resulting of COVID-19 can also impact metabolism leading to drug-disease
171 interaction. However, this phenomenon might be stronger in the later stage of infection (i.e the
172 cytokine storm) than at the early stage, where nirmatrelvir/ritonavir is indicated.

173

174 **2.1 CYP3A**

175 Ritonavir is metabolized by CYP3A4 with a Km value of around 20 µM. However, the KI value for
176 CYP3A4-mediated drug metabolism is 0.015 µM [13]. Ritonavir's potent inhibitory potential is-based
177 on the efficient blocking of CYP3A4 and CYP3A5 (kinact/KI) and was reported to be as large as 3200
178 and 667 min-1·mM-1], respectively [14]. Studies have shown that ritonavir is a type II ligand that
179 perfectly fits into the CYP3A4 active site and irreversibly binds to the heme iron via the thiazole

6

180 nitrogen. This binding results in decreased redox potential of the CYP protein [15]. This is the basis of
181 the DDI between ritonavir and immunosuppressant drugs such as tacrolimus, ciclosporin, everolimus
182 and sirolimus that are metabolized by CYP3A. Enzymatic activity can only be restored through *de*
183 *novo* protein synthesis; therefore, these mechanism-based inhibitions are prolonged *in vivo* and are
184 observed even after stopping the inhibitors.

185

186 Ritonavir is well acknowledged as a strong CYP3A inhibitor with an inhibitory effect starting from the
187 first intake and lasting at least 3 days after the end of ritonavir administration. Therefore, ritonavir
188 has been combined with other drugs as a pharmacokinetic booster such as the prescription for anti-
189 human immune deficiency virus (HIV) drug and direct acting antiviral (DAA) drug against hepatitis C
190 virus (HCV). Studies have demonstrated drug interactions with the DAA combination of ombitasvir,
191 paritaprevir and ritonavir (Viekirax®) and 11 medications in healthy volunteers [16]. While only
192 formulated with ritonavir 100 mg once daily, the exposure of ketoconazole, digoxin, pravastatin and
193 rosuvastatin with Viekirax® were increased by up to 105%, 58%, 76% and 161%, respectively, while
194 omeprazole exposure decreased by approximately 50%. However, during this DDI phase II study, no
195 clinically meaningful changes in ombitasvir, paritaprevir and ritonavir exposures were observed in
196 the presence of the 11 medications.

197

198 **2.2 P-glycoprotein**

199 Ritonavir is unidirectionally transported by P-gp [17, 18]. Several clinical studies have shown that
200 ritonavir pre-treatment in healthy subjects slightly decreased renal and non-renal clearance of
201 digoxin administered orally or intravenously [19, 20]. However, compared with rifampin, digoxin
202 renal clearance was only reduced with ritonavir pre-treatment. In addition, simultaneous rifampin
203 administration increased the Cmax, AUC0-4 and AUC0-24, while diminished digoxin renal clearance,
204 suggesting cis-inhibition on hepatic influx transporter and renal P-gp. The simultaneous
205 administration of ritonavir increased Time to peak concentration (tmax) and AUC0-24, and lowered
206 digoxin renal clearance, implying that ritonavir mainly affects digoxin's tubular secretion via P-gp
207 [21]. Taken together, ritonavir administration would affect mainly the transport activity of renal P-gp
208 and may only minimally decrease the intestinal and liver P-gp activity following saturation of CYP3A
209 enzyme. This implies minimal impact of ritonavir on ISD interaction mediated through P-gp.

210

211 **2.3 Additional**

212 Ritonavir is a strong activator of the pregnane X receptor (PXR), which regulates the expression of
213 various metabolic enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19 and uridine diphospho-
214 glucuronosyltransferases (UGTs) [12]. The activities of CYP2C8, CYP2D6, organic anion transport
215 protein (OATP), and breast cancer resistance protein (BCRP), are decreased in the presence of
216 ritonavir [12, 17].

217

218 **3.   Nirmatrelvir/ritonavir with calcineurin inhibitors**

219 The calcineurin inhibitors (CNIs) tacrolimus and ciclosporin are both narrow therapeutic index drugs
220 [22]. For organ transplant recipients target concentrations of CNIs have been defined, depending on

7

221 immunological risk, time after transplantation, co-treatment with other immunosuppressant drugs
222 and other factors [23]. DDI are frequent, as ciclosporin and tacrolimus are metabolized by CYP3A
223 enzymes (in gut wall and liver) and they are also substrates of P-gp [24], which is expressed at high
224 levels in the liver, gastrointestinal tract, and kidney [25].

225

226 A formal DDI study in healthy volunteers showed that in the presence of steady-state concentrations
227 of ritonavir (100 mg once daily) the dose-normalized ciclosporin concentration at 24 hours (C24),
228 and area under the concentration-time curve from time 0 to infinity (AUCi) were 15.8-fold and 5.8-
229 fold higher, respectively [26]. The effect on tacrolimus pharmacokinetics was even more drastic with
230 a 17-fold and 57-fold rise in dose-normalized tacrolimus C24 and AUCi, accordingly. The half-lives of
231 ciclosporin and tacrolimus increased from 7 to 25 h and 32 to 232 h, correspondingly. For both CNIs
232 the effect on Cmax was smaller, indicating that the reduced clearance by the liver as more likely the
233 primary mechanism of the interaction than increased oral bioavailability. Thus, these results
234 suggests that CYP3A inhibition, rather than P-gp, is the primary mechanism of this interaction.
235 Keeping the same dose of tacrolimus following initiation ritonavir treatment will lead to an
236 extremely high tacrolimus exposure within 24 hours. There is a need for a significant dose reduction,
237 to avoid potentially toxic concentrations. For anti-HIV therapies in the context of liver
238 transplantation, it has been suggested that a dose reduction of tacrolimus as low as 0.5 or 1.0 mg
239 once a week when co-administered with ritonavir boosted lopinavir therapy is necessary [27].

240

241 Drug interaction with both CNIs is significant and may lead to toxic concentrations of CNIs for a
242 prolonged period of time; however, monitoring of the magnitude of the interaction through drug
243 concentration measurements can provide a way to manage this potentially dangerous interaction in
244 those patients who may simultaneously need both drugs.

245

246 **3.1 Recommendations**

247 **3.1.1 Tacrolimus**

248 For most patients, it seems best to discontinue tacrolimus 12h before nirmatrelvir/ritonavir therapy
249 is started. The pre-dose concentration measured at the time of starting nirmatrelvir/ritonavir is
250 expected to be maintained at about 75% of the initial concentration at the end of the 5 days of the
251 antiviral treatment, whereas the magnitude of change in tacrolimus total exposure (AUC_{0-120h}) has
252 been more difficult to estimate. On the other hand, in the context of an active COVID-19, a small
253 reduction in the exposure of the ISD may contribute to faster viral clearance. If possible, we
254 recommend a "keep it simple" approach and discontinue tacrolimus during the entire 5-days of
255 antiviral treatment with nirmatrelvir/ritonavir.

256

257 A less radical alternative and intended only for high-risk patients (patients in the early post-
258 transplant period or those with a high risk of rejection) would be to administer a small tacrolimus
259 dose (one eighth of standard dose) on day 1 of nirmatrelvir/ritonavir therapy (with no further dosing
260 for the next five days at least) to maintain a certain level of tacrolimus exposure during the next
261 consecutive 5 days of nirmatrelvir/ritonavir therapy. This approach also has the advantage of

262 maintaining an exposure (considering AUC_{0-120h}) after antiviral treatment initiation closer to the
263 exposure provided by the patients' initial dosage before nirmatrelvir/ritonavir initiation. Such a
264 strategy should be supported by a close collaboration between pharmacologists and clinicians (table
265 1).

266

267 Upon discontinuation of nirmatrelvir/ritonavir, CYP3A activity will recover with time. The half-life or
268 ritonavir is short (3-5 hours), but published data suggest that it may take 3 days for the CYP3A
269 activity to completely restore, achieving after 48h almost 75% of the metabolic activity [28].
270 Therefore, a pragmatic approach would be to extend the temporary discontinuation of tacrolimus
271 treatment with a few more days with tacrolimus exposure under close surveillance of and cautious
272 dosing. After 7-8 days tacrolimus can be reintroduced, either in the dose given prior
273 nirmatrelvir/ritonavir treatment or based on measured tacrolimus concentrations at the time of re-
274 starting tacrolimus treatment (as suggested by Lange et al. [29]).

275

276 **3.1.2 Ciclosporin**

277 For ciclosporin the impact of ritonavir is somewhat smaller than for tacrolimus. Nevertheless,
278 ciclosporin over-exposure accompanied by signs of severe nephrotoxicity has been reported in
279 patients on ritonavir [30]. Following nirmatrelvir/ritonavir introduction, the total daily dose of
280 ciclosporin should be reduced to 20% of the initial dose and administered once daily to maintain
281 similar blood ciclosporin concentrations. This degree of dose reduction is comparable to what has
282 been described with direct antiviral agents [26, 31]. Regular ciclosporin concentration monitoring is
283 advised to guide dosing, especially after discontinuation of nirmatrelvir/ritonavir (table 1).

284 Therapeutic monitoring (TDM) of tacrolimus and ciclosporin is advised to guide safe dosing (see
285 dedicated section).

286

287 **4. Nirmatrelvir/ritonavir with mTOR inhibitors: everolimus, sirolimus**
288 To date there are no reports on the optimal dosing strategy for mTOR inhibitors (mTORi mechanistic
289 target of rapamycin) like everolimus and sirolimus, when combined with nirmatrelvir/ritonavir or
290 other ritonavir formulations. In the clinical trials that were performed, patients who used
291 medications that are highly dependent on CYP3A4 for clearance such as sirolimus and everolimus
292 were excluded. To provide tentative dose adjustments for solid organ transplant recipients on
293 mTORi when starting on nirmatrelvir/ritonavir, we therefore need to rely on the information from
294 drug interactions which have similar properties with respect to CYP3A mediated metabolism and P-
295 gp mediated transport inhibition. For everolimus and sirolimus there are only a small number of
296 retrospective reports that could provide guidance to what would be the appropriate dosing strategy.
297 A study of sirolimus dosing requirement in patients on HIV therapy with ritonavir combination, 1/10
298 to 1/20 of the typical dose of sirolimus has been recommended [32].

299

300 In a cross-over study of 12 healthy subjects, a single oral everolimus dose of 2 mg was given on day 1
301 under fasting conditions. Starting on day 10, ketoconazole 200 mg was administered orally every 12
302 hours and four days later (day 13) everolimus was given again, at a dose of 1 mg. When the results

9

303   were normalized to a 2 mg dose for comparison, the Cmax increased on average 3.9-fold (90% CI,
304   3.4-4.6) while AUC increases were clustered largely in the range from 11.2-fold to 17.5-fold (n = 11)
305   with ketoconazole. The average increase in AUC across all subjects was 15.0-fold (90% CI, 13.6-16.6).
306   Everolimus half life increased from an average of 30 (SD=4) to 56 (SD=5) h [33]. Although the results
307   were obtained with the combination of ketoconazole and not with ritonavir, they indicate the
308   potential influence of CYP3A4 and P-gp inhibition on changing in everolimus exposure. It is expected
309   that the effect of ritonavir will be much greater.

310

311   A 35-year-old patient with COVID-19 developed a very high everolimus concentration during co-
312   treatment with lopinavir/ritonavir (400/100 mg BID). The everolimus dose was initially reduced by
313   1/3 but pre-dose concentrations reached a maximum of 31.1 ng/mL. The authors recommended
314   immediate withdrawal of mTORi therapy and close monitoring of blood concentrations, clinical
315   status, and signs of drug toxicity [34].

316

317   A recent study included adult transplant recipients treated with nirmatrelvir/ritonavir for five days,
318   among these patients, 3 were on everolimus and 1 on sirolimus [35]. According to the protocol [29],
319   the mTORi was withheld at the start of nirmatrelvir/ritonavir. The most recent mTORi pre-dose
320   concentration had been measured 77 days (IQR, 58 - 140) before the start of nirmatrelvir/ritonavir
321   and these concentrations averaged 4.8 ng/mL (IQR, 3 - 4.9). After completion of the
322   nirmatrelvir/ritonavir, two patients had undetectable concentrations on day 7 and day 9 while the
323   third patient had 1.4 ng/mL on day 8. The patient on sirolimus had a trough concentration of 5
324   ng/mL 13 days prior to starting nirmatrelvir/ritonavir and 9.5 ng/mL on day 14. Another case report
325   advised sirolimus dosage reductions to 1.5 mg per week and 1 mg per 14 days [36].

326

4.1 Recommendations

328   Based on these very limited observations, the following is recommended for the dosing of mTORi
329   during and following nirmatrelvir/ritonavir treatment:

330   •   Approximately 12 hours before nirmatrelvir/ritonavir initiation, the mTORi should be put on
331   hold. From the day after cessation of nirmatrelvir/ritonavir, the mTORi may be re-introduced
332   in one fifth of the original dose, and the dose may be increased by twenty percent each day
333   or according the measured mTORi trough concentrations [37]. The timing and selection of
334   dose for re-introduction of the mTORi may also depend on which combination of other
335   immunosuppressants are used and how important the contribution from mTORi in the
336   immunosuppressive regimen.

337

338   Alternatively, if it is considered important to avoid subtherapeutic mTORi concentrations, and given
339   the low risk of immediate adverse drug reaction with these drugs, another strategy that can be
340   considered is as follows:

- A microdose of 1/8th of the patient's initial daily dose should be given on days 1, 3 and 5 after starting nirmatrelvir/ritonavir, and the initial treatment dosage could be restarted on day 7 (table 1).

It is recommended to frequently monitor immunosuppressant drug levels, at least right before dose administration and shortly after the end of nirmatrelvir/ritonavir treatment (see dedicated section).

5. Nirmatrelvir/ritonavir with mycophenolic acid

Mycophenolic acid (MPA), administered as a prodrug (mycophenolate mofetil, the morpholinoethylester of MPA) or an enteric-coated salt (mycophenolate sodium), is one of the most important drugs for the immunosuppressive regimen in organ transplant recipients. During viral infections, MPA is usually the first immunosuppressive drug, which dosage is decreased if not discontinued [38]. The drug has also been shown to strongly decrease SARS-CoV-2 vaccine efficacy [39]. Therefore, therapeutic management of transplant recipients infected with SARS-CoV-2 requires careful review and a special consideration should be given to potential interactions with approved COVID-19 treatments like nirmatrelvir/ritonavir.

The metabolism of MPA is extensive and mostly occurs in the liver, intestine, and kidney through the uridine 5'-diphospho-glucuronosyltransferase (UGT) system. The main UGT isoforms involved in MPA glucuronidation are UGT1A9 and 2B7 [40, 41]. The glucuronidation pathway produces a major metabolite, MPA 7-O-glucuronide (MPAG), which is inactive. A minor phase 1 metabolite from human cytochrome P450 isoforms, CYP3A4 and CYP3A5, the 6-O-desmethyl-MPA (DM-MPA) and its related glucuronide were also identified in blood and urine from transplant patients [42].

Expected DDI with nirmatrelvir/ritonavir, may result from ritonavir being an inhibitor and inducer of UGT. Different studies have underscored the distinct effects of ritonavir on UGT isoforms. Ritonavir has been shown *in vitro* to consistently inhibit UGT1A1, UGT1A3 and UGT1A4 and weakly inhibit UGT1A6, UGT1A9 and 2B7 (IC_{50}>100µM) [43]. On the other hand, ritonavir has been shown to induce UGTs, in clinical studies as it significantly decreased systemic exposure to some drugs eliminated from the body by the glucuronidation pathway like ethinyl oestradiol [44]and lamotrigine [45].

Ritonavir seems to only weakly interact with UGT isoforms (1A9 and 2B7) involved in MPA metabolism as evidenced by the absence of significant modification in AUC in a hepatitis C virus-infected patient treated with the combination of ombitasvir, paritaprevir/ritonavir, dasabuvir and MPA for vasculitis [46]. Moreover, a successful recovery from COVID-19 has been reported in a patient with systemic lupus erythematosus treated concomitantly with lopinavir/ritonavir and the SLE drugs including mycophenolic acid [47]. Overall, a limited impact of nirmatrelvir/ritonavir is expected on MPA metabolism and exposure.

11

5.1 Recommendations

Given the short duration (5 days) of nirmatrelvir/ritonavir treatment, and because of the low potential pharmacokinetic interaction, there is no need to adjust MPA dose from an exposure point of view. However, in solid organ transplant patients with COVID-19 the first drug to be temporarily discontinued to allow clearance of the virus is MPA (table 1).

6. Nirmatrelvir/ritonavir with corticosteroids

Corticosteroids are an integral part of induction and maintenance immunosuppressive regimens in solid organ transplantation. Corticosteroids are also a drug category that is used in acute therapy but at the severe, advanced stage of COVID-19 infection. Prednisone, prednisolone and methylprednisolone are the most commonly used synthetic corticosteroids in transplant recipients. Prednisone is a prodrug converted through first-pass metabolism by 11-β-hydroxydehydrogenase to its active form, prednisolone [48].

Both prednisolone and prednisone undergo 6β-hydroxylation via the CYP3A4 metabolic pathway and are inducers of multidrug associated resistance protein 2 (MRP2), as well as substrates, inhibitors, and inducers of P-gp [49, 50]. Corticosteroid clearance has been reported to be significantly reduced in patients on ritonavir-boosted protease inhibitors resulting in increased concentration [51]. In these patients, the higher exposure has been associated with bone toxicities (e.g., osteonecrosis) and Cushing syndrome [52]. In the French Pharmacovigilance Database, antiretroviral-boosting agents in combination with corticosteroids were incriminated in several cases of iatrogenic Cushing syndrome but this has only been reported in chronic treatment and is unlikely to happen during a 5-day treatment course with ritonavir [53].

6.1 Recommendations

Nirmatrelvir/ritonavir combination with corticosteroids in transplant patients could presumably lead to a temporary increase in prednisolone exposure due to CYP3A4 and P-glycoprotein inhibition. We recommend maintaining the same dosage of corticosteroid during the 5-day nirmatrelvir/ritonavir course (table 1).

7. Therapeutic drug monitoring of immunosuppressive drugs with nirmatrelvir/ritonavir

7.1 TDM recommendations for CNIs to modulate DDIs with COVID-19 PI-based treatment.

The primary objective of TDM is to minimize the toxicity of immunosuppressant drugs while preventing any under- and over-immunosuppression possibly leading to graft rejection due to improper discontinuation of or of immunosuppression, or toxicity, respectively. Here we provide some general guidance for monitoring patients simultaneously on nirmatrelvir/ritonavir and ISDs. They are also summarized in table 1.

When tacrolimus is discontinued before the antiviral treatment, as proposed in these recommendations, there is limited risk of toxicity. Given the fact that nirmatrelvir/ritonavir

12

421 treatment has been designed for outpatient, it is possible to avoid TDM during the 5-day course
422 unless there's a safe way to apply it (ideally auto-sampling at home).

423

424 The same conclusion can be formulated for ciclosporin. It is important to note that blood
425 concentration vs time curve of CNIs combined with ritonavir is flat, with a low Cmax (related to the
426 low dose) and an almost horizontal slope (given the long half-life). As a result, the relationship
427 between the pre-dose concentration and the AUC is different from the situation where CNI is taken
428 twice daily in a much higher dose. The mean AUC in ritonavir treated patients was 40 % lower
429 compared with the AUC's patients not co-treated with ritonavir, when similar trough levels were
430 targeted [54].

431

432 In case of using small tacrolimus boost (one eighth of standard dose corresponding to a 40-fold dose
433 reduction with respect to the five previous days of tacrolimus treatment) on day 1 of
434 nirmatrelvir/ritonavir therapy, for hospitalized patients, patients at high-risk of rejection or at the
435 initial post-operative period, a more comprehensive TDM approach can be proposed. This may
436 include early two-sample points (e.g. just before starting nirmatrelvir/ritonavir, at the end of day-1
437 and day-2) to capture the elimination rate constant of the drug, inform patient's exposure by
438 approximating the AUC and help defining the time to restart drug dosing. This approach will prevent
439 toxic tacrolimus exposure and minimize levels falling below the target concentrations. For tacrolimus
440 and ciclosporin TDM, the trough concentration is more feasible to obtain but the AUC may better
441 reflect the impact of DDIs in the whole PK profile [23]. These patients may benefit from limited
442 sampling strategy, with Bayesian estimation of the total AUC, and dried blood spot analysis should
443 be considered, particularly for tacrolimus [55, 56].

444

445 Given that 70-90% of CYP3A enzyme activity can be expected to recover at day+3 after ritonavir
446 discontinuation of nirmatrelvir/ritonavir, TDM can also be proposed at the time of CNI treatment
447 restoration or shortly thereafter. If the treatment with nirmatrelvir/ritonavir would be continued for
448 a much longer time than just 5 days, it would make sense to aim for higher pre-dose target
449 concentrations [57].

450

451 **7.2 TDM recommendations for mTORi to modulate DDIs with COVID-19 PI-based treatment.**

452 For sirolimus and everolimus similarly to tacrolimus in terms of interactions with boosted PIs are
453 expected although less-well defined [32]. If mTOR is withdrawn, ideally, mTOR concentrations
454 should be monitored before starting the antiviral drug. Further dose adjustments will be necessary
455 to reach target concentrations. In case of using a microdose of 1/8th of the patient's initial daily dose
456 given on day-1, -3 and -5, trough concentration may be measured on day-3 of antiviral treatment to
457 potentially adjust the subsequent dose. In any case, when mTORi is re-introduced, trough
458 concentrations should be monitored every second day until stable on a fixed dose and mTORi should
459 be restarted according to the TDM results. If out of therapeutic range, measurements should be
460 repeated until concentration is within range and then mTORi dose restarted or adjusted [58]. Again,

461 the implementation of TDM in an outpatient setting can be facilitated using a microsampling
462 approach.

463

464 **7.3 TDM recommendations for mycophenolic acid to modulate DDIs with COVID-19 PI-based**
465 **treatment.**

466 If mycophenolic acid treatment is maintained during the antiviral therapy, TDM can be performed, if
467 needed, according to locally practice. This would help generating more data on this topic, including
468 careful descriptions of case reports. Until such data are available, TDM might be a useful tool to
469 maintain adequate exposure of MPA, for example by using a limited sampling strategy or a Bayesian
470 approach [58].

471

472 **8. Conclusion**

473 Combining nirmatrelvir/ritonavir with narrow therapeutic index drugs metabolized by CYP3A4 and P-
474 gp is challenging. This is particularly true for tacrolimus and to a lesser extent for ciclosporin,
475 everolimus and sirolimus. Data from DDI studies between ISD and potent CYP3A4 inhibitors obtained
476 in the field of HIV and HCV enables the generation of recommendations for dosage adjustments for
477 these drugs and to secure their prescription during antiviral treatment. While not easy to implement
478 in an outpatient setting, TDM may be a useful tool to confirm that drug adjustments are appropriate
479 in a specific case and to help reintroducing ISDs at the end of nirmatrelvir/ritonavir treatment. A
480 TDM approach during the treatment also appears appropriate when a strict drug exposure
481 conservation must be ensured.

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Table 1. Recommendations for immunosuppressive drugs adjustment when combined with nirmatrelvir/ritonavir, for restart strategies of the immunosuppressive drugs and proposed therapeutic drug monitoring.

AUC: area under the curve of drug concentrations; TDM: therapeutic drug monitoring.

Immunosuppressive agent	Recommended immunosuppressive drug adjustment	Alternative immunosuppressive drug adjustment	Restart of the immunosuppressive drug	Proposition for TDM (if feasible)
Tacrolimus	Discontinue tacrolimus 12h before nirmatrelvir/ritonavir initiation	Administer 1/8th of the usual daily dose on day-1 and then discontinue	Tacrolimus can be reintroduced on day-7/8	Two sample time points to capture drug elimination and TDM at treatment restoration or shortly thereafter (if possible an AUC monitoring should be conducted)
Cyclosporine	Reduced to 20% of the initial dose from day-1	-	Progressively reintroduced from day-6	Trough concentrations (be aware that pharmacokinetic profile can change during the antiviral treatment) and TDM at treatment restoration or shortly thereafter
m-TOR inhibitors	Discontinue m-TOR inhibitor 12h before nirmatrelvir/ritonavir initiation	Administer 1/8th of the usual daily dose on day-1, -3 and -5	m-TOR can be reintroduced on day-7	Trough concentrations (on day-3 in case of applying the alternative drug adjustment) and then TDM at treatment restoration or shortly thereafter
Mycophenolic acid	No need to adjust drug dosage given the short antiviral treatment duration	Mycophenolic acid can be discontinued in some cases	-	TDM according to local practice
Corticosteroids	No need to adjust drug dosage	-	-	No need for TDM