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## Abstract:

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

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

## 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 (1*R*,2*S*,5*S*)-*N*-((1*S*)-1-Cyano-2-((3*S*)-2- oxopyrrolidin-3-yl)ethyl)-3-((2*S*)-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].

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.

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

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

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

## 2. Drug-drug interaction with ritonavir-boosted nirmatrelvir

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

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

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

### 2.1 CYP3A

Ritonavir is metabolized by CYP3A4 with a Km value of around 20 µM. However, the KI value for CYP3A4-mediated drug metabolism is 0.015 µM [13]. Ritonavir's potent inhibitory potential is-based on the efficient blocking of CYP3A4 and CYP3A5 (kinact/KI) and was reported to be as large as 3200 and 667 min-1·mM-1], respectively [14]. Studies have shown that ritonavir is a type II ligand that perfectly fits into the CYP3A4 active site and irreversibly binds to the heme iron via the thiazole nitrogen. This binding results in decreased redox potential of the CYP protein [15]. This is the basis of the DDI between ritonavir and immunosuppressant drugs such as tacrolimus, ciclosporin, everolimus and sirolimus that are metabolized by CYP3A. Enzymatic activity can only be restored through *de novo* protein synthesis; therefore, these mechanism-based inhibitions are prolonged *in vivo* and are observed even after stopping the inhibitors.

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

### 2.2 P-glycoprotein

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

### 2.3 Additional

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

## 3. Nirmatrelvir/ritonavir with calcineurin inhibitors

The calcineurin inhibitors (CNIs) tacrolimus and ciclosporin are both narrow therapeutic index drugs [22]. For organ transplant recipients target concentrations of CNIs have been defined, depending on immunological risk, time after transplantation, co-treatment with other immunosuppressant drugs and other factors [23]. DDI are frequent, as ciclosporin and tacrolimus are metabolized by CYP3A enzymes (in gut wall and liver) and they are also substrates of P-gp [24], which is expressed at high levels in the liver, gastrointestinal tract, and kidney [25].

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

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

## 3.1 Recommendations

### 3.1.1 Tacrolimus

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

A less radical alternative and intended only for high-risk patients (patients in the early post-transplant period or those with a high risk of rejection) would be to administer a small tacrolimus dose (one eighth of standard dose) on day 1 of nirmatrelvir/ritonavir therapy (with no further dosing for the next five days at least) to maintain a certain level of tacrolimus exposure during the next consecutive 5 days of nirmatrelvir/ritonavir therapy. This approach also has the advantage of maintaining an exposure (considering $AUC_{0-120h}$) after antiviral treatment initiation closer to the exposure provided by the patients' initial dosage before nirmatrelvir/ritonavir initiation. Such a strategy should be supported by a close collaboration between pharmacologists and clinicians (table 1).

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

### 3.1.2 Ciclosporin

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

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

## 4. Nirmatrelvir/ritonavir with mTOR inhibitors: everolimus, sirolimus

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

In a cross-over study of 12 healthy subjects, a single oral everolimus dose of 2 mg was given on day 1 under fasting conditions. Starting on day 10, ketoconazole 200 mg was administered orally every 12 hours and four days later (day 13) everolimus was given again, at a dose of 1 mg. When the results were normalized to a 2 mg dose for comparison, the Cmax increased on average 3.9-fold (90% CI, 3.4-4.6) while AUC increases were clustered largely in the range from 11.2-fold to 17.5-fold (n = 11) with ketoconazole. The average increase in AUC across all subjects was 15.0-fold (90% CI, 13.6-16.6). Everolimus half life increased from an average of 30 (SD=4) to 56 (SD=5) h [33]. Although the results were obtained with the combination of ketoconazole and not with ritonavir, they indicate the potential influence of CYP3A4 and P-gp inhibition on changing in everolimus exposure. It is expected that the effect of ritonavir will be much greater.

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

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

### 4.1 Recommendations

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

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

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

- A microdose of 1/8$^{th}$ 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.

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

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

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

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

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

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

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

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

## 8. Conclusion

Combining nirmatrelvir/ritonavir with narrow therapeutic index drugs metabolized by CYP3A4 and P-gp is challenging. This is particularly true for tacrolimus and to a lesser extent for ciclosporin, everolimus and sirolimus. Data from DDI studies between ISD and potent CYP3A4 inhibitors obtained in the field of HIV and HCV enables the generation of recommendations for dosage adjustments for these drugs and to secure their prescription during antiviral treatment. While not easy to implement in an outpatient setting, TDM may be a useful tool to confirm that drug adjustments are appropriate in a specific case and to help reintroducing ISDs at the end of nirmatrelvir/ritonavir treatment. A TDM approach during the treatment also appears appropriate when a strict drug exposure 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 1/8$^{th}$ 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 1/8$^{th}$ 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 |