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Review

What is New in Prophylaxis and Treatment of Covid- 19 in Renal Transplant Patients?

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Abstract: Kidney transplant recipients, because of a weak immune response due to the assumption of immunosuppressant are exposed to the risk of COVID-19 infection. This fact realize the problem on how to treat the severe infection without carrying the risk of acute rejection due to the reduction of the immunosuppressive drugs.The best are the prophylactic measures to be taken before transplantation as vaccination. If the patient is already transplanted, three measures may be undertaken: Vaccination, use of monoclonal antibodies, use of therapeutic antiviral small molecules. Concerning vaccination is still debated which one is the best and how many doses should be given. The surge of new virus variant is the major problem and invites to find new active vaccines. In addition, not all the transplanted patients develop antibodies. The other measure is the use of monoclonal antibodies. They may be used as prophylaxis or in the early stage of the disease. Finally, the antiviral small molecules may be used again as prophylaxis or treatment. Their major drawback are the interference with the immunosuppressive drugs and the fact that some of them cannot be administered to patients with low eGFR.

Keywords: COVID-19 prophylaxis; COVID-19 treatment; Kidney transplantation; Vaccination; Monoclonal antibodies; Small antivirus molecules

INTRODUCTION

Kidney transplant (KTx) recipients affected by COVID-19 infection present several challenges principally concerning prophylaxis and therapy.

SARS-CoV-2 has a great impact on immunocompromised individuals with multiple comorbid conditions as is common in KTx recipients.

A severe disease in immunocompromised individuals may reflect the inability to mount an effective immune response also after vaccination (1).

The assessment of which individuals will benefit from monoclonal antibodies and small molecular therapeutics are complicated by an incomplete understanding of the thresholds for a protective immunity.

Moreover, in transplant patients a discordance exists between cellular and immune responses.

In addition, in the immunodominant spike (S) protein, 5016 different amino acid replacements or substitutions have been identified as well as multiple deletions may be present. As variant emerged, natural antibodies, therapeutic monoclonal and some vaccine-elicited antibodies have become less effective in preventing disease progression (2).

Overall, in a first time the mutation rates were thought to be rather low, but later it was well recognized that spike protein mutations by an altered membrane fusion of virus and host cells led to either an altered pathogenicity and human to human spread, an altered susceptibility to vaccine induced immunity and an altered response to monoclonal and small molecule therapeutics.

Additionally, multiple studies identified several variables associated with poor humoral immune response, among which older age, high dose assumption of corticosteroids

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in the last 12 months, triple immunosuppression, and the use of mycophenolate mofetil and of belatacept.

In this study, we will examine new approved therapies with particular reference to:

a) Vaccination
b) Monoclonal antibodies, examining pre-exposure prophylaxis with tixagevimab and cilgavimab (Eurisheld) and others monoclonal and polyclonal antibody products.
c) Small antiviral proteins as Nirmatrelvir/ritonavir, Molnupivar and Remdesivir (RMD) with particular concern for their interaction with immunosuppressive agents.

VACCINATION

In normal condition, after vaccination the immune response includes: neutralizing antibodies that inhibit binding of virus to the receptor; T cell responses that are detectable either after vaccination and natural infection. Antibodies have a main function in preventing infection; T cells and antibodies both contribute to the prevention of a severe disease.

Two wide studies documented firstly the efficacy and safety of two mRNA SARS-CoV-2 vaccines.

In one study, 43548 participants underwent randomization to receive BNT162b2 or placebo (3). The conclusion of the study was that a two-dose regimen of BNT 162b2 conferred 95% protection against COVID-19. A different study, evaluated safety and efficacy of the mRNA-1273 vaccine. This vaccine is a lipid nanoparticle-encapsulated mRNA that encodes the full-length spike protein of SARS-CoV-2 virus. The study was conducted in 99 centers in the United States involving 30420 subjects assigned 1:1 to receive either vaccine or placebo (4). The mRNA-1273 vaccine had an efficacy of 94.1% in preventing COVID-19.

Both studies were conducted in non-transplanted and healthy subjects and against the Delta variant of the virus.

In a different study, Hamm et al (5) documented a decline in antibody concentrations 6 months after two doses of SARS-CoV-2 BNT162b2 vaccine both in solid organ transplant (SOT) recipients and in healthy controls. The decline of both cellular and humoral responses was higher in transplanted patients with respect to healthy subjects and risk factors for the decline were older age, treatment with mycophenolate, treatment with corticosteroids. The decline was higher in KT recipients with respect to other SOT recipients.

Another study (6) conducted a systematic review and a meta-analysis to compare the seroconversion rate with two doses of BNT162b2 versus mRNA-1273 in SOT recipients. The conclusion of the study was that in SOT recipients a higher conversion rate was observed after vaccination with mRNA-1273 compared to BNT162b2 (figure 1). The authors concluded that further studies are needed to verify whether this difference is confirmed after a third dose vaccination.

A study from Liefeldt (7) examined the predictors of serological response to SARS-CoV-2 vaccination in kidney transplant patients. The study found that predictors of a weak response were age at vaccination, time after kidney transplantation, immunosuppression, estimated glomerular filtration rate (eGFR) at vaccination and lymphocyte count at vaccination (table 1). The use of mycophenolate further impaired the response to vaccination and the authors hypotized that erythrocyte IMPDH activity could be used to monitoring mycophenolate treatment.

Table 1. Multivariate analysis of factors associated with serological response to vaccination after kidney transplantation.

	Multivariate analysis		
Factors	OR	95%CI	p Value
Age at 2nd vaccination	0.98	0.96; 1.00	0.039
Time after kidney TX	1.06	1.02; 1.10	0.001

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TAC + MPA + Steroid	0.15	0.08; 0.28	<0.001
CyA + MPA + Steroid	0.51	0.27; 0.96	0.038
TAC/CyA + Steroid	4.11	1.71; 9.90	0.002
eGFR at vaccination	1.03	1.02; 1.04	<0.001
Lymphocyte count at vaccination	1.12	1.06; 1.18	<0.001
CNI trough levels at vaccination	0.94	0.90; 1.00	0.036

Abbreviation: OR = odd ratio; CI = confidence interval; TAC = Tacrolimus; MPA = Mycophenolate acid; CyA = Cyclosporine; eGFR = estimated glomerular filtration rate; CNI = calcineurine.

Another study from Balsby et al (8) found that the antibody response after a third dose of BNT162b2 was improved, but the overall response was still low with a significant ratio of non-responders. The predictors of a poor response were similar to those found in other studies. The KTx recipients were confirmed to be the lower responders (figure 2).

A study of Hod et al (9) documented the relevance of a third booster dose of BNT162b2. The study documented that a third dose increases both neutralizing antibodies and receptor binding domain (RBD) antibodies in KTx patients. The results of both responders and non-responders are shown in table 2.

Table 2 Univariate analysis for immune status before the third vaccine vs post third vaccine in RTR.

	Before 3rd vaccine	Post 3rd vaccine	p value
All cohort			
IgG-RBD GMT (95% CI)	0.79 (0.65-0.96)	3.08 (2.76-3.45)	<0.0001
NA GMT (95% CI)	17.46 (12.38-24.62)	362.2 (220.7-594.6)	<0.0001
Positive responders			
N (%)	32 (32.3)	85 (85.9)	<0.0001
= 35IgG-RBD GMT (95% CI)	2.53 (2.07-3.11)	3.57 (3.28-3.88)	<0.0001
NA GMT (95% CI)	89.12 (53.03-149.8)	689.9 (456.3-1043)	<0.0001
Negative responders			
N (%)	67 (67.7)	14 (14.14)	<0.0001
IgG-RBD GMT (95% CI)	0.45 (0.39-052)	1.28 (0.87-1.86)	<0.0001
NA GMT (95% CI)	8.01 (5.92-10.84)	7.25 (2.42-21.71)	0.85

Abbreviations: CI = Confidence interval; GMT = Geometric mean titre; NA = Nreutralizing antibodies; RBD = Receptor binding domain.

A recent systematic review and meta-analysis (10) documented again the immunogenicity and risk factors associated with poor humoral immune response to any SARS-CoV-2 vaccines in SOT recipients. Overall, 112 studies have been included in the meta-analysis with 11713 SOT recipients. The antibody response both for anti spike antibodies and for neutralizing antibodies were higher according the number of vaccines. The factors principally associated with a poor antibody response were older age, deceased donor, antimetabolite use, recent rituximab use and recent antithymocyte globulin exposure.

Several studies (11, 12) document the low immunization rate that occurs in several subjects receiving two doses of the mRNA-1273 SARS-CoV-2 vaccine. Among these are kidney transplant recipients as documented by the study of Benotmane et al (11). Other patients with a weak humoral immune response are older patients. The weak response occurs both after naïve COVID-19 infection and after BNT162b2 vaccination (12). The study also suggests that in these patients, vaccination after infection may be useful because it maintains a higher antibody titer for a large period.

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A recent study from Mazzoni et al (13) have documented that SARS-CoV-2 infection and vaccination trigged long-live B cells and CD4 lymphocytes. Either in patients vaccinated after recovering from a COVID-19 infection and in patients vaccinated naïve there is a significant decrease in all antibody levels, even if the decline is more pronounced in naïve individuals. The decline is detectable after 8 months from vaccination or from COVID-19 infection. Memory cells are still detectable after 8 months. The decrease in humoral immunity may account for reinfections. A third (booster dose) restores the humoral activity in vaccinated subjects, while the need of a booster dose is still object of discussion for previously infected patients. The results of this study confirm previous studies, which documented similar data (14, 15, 16,17).

Interesting data are also documented by the already cited study of Hamm (5). Previous studies had already documented a reduced humoral response after two vaccine doses in SOT recipients (18, 19, 20, 21). The Hamm study evaluates the antireceptor binding domain (RBD) immunoglobulins after two doses of BNT162b2 in SOT recipients versus controls and confirmed the reduced immunological response in SOT recipients. In addition, the response is weaker in KTx recipients than other transplants.

In conclusion, in SOT recipients the two doses vaccination has a low immunogenicity (22).

A randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients was made by Hall et al. (23). The study documented an increase in anti RBD antibodies, an increase in neutralizing antibodies and an increase in polifunctional CD4 T cells after the third dose in SOT recipients.

The beneficial effect of three vaccine doses was documented by the study of Kamar et al (24) who documented a relevant increase of anti SARS-CoV-2 antibodies after three doses of the mRNA vaccine BNT162b2. (figure 3).

In a different study, Kamar et al. (25) documented the efficacy of three doses of vaccine (BNT162b2) in 850 SOT recipients. The study evaluated the anti-SARS-CoV-2 spike protein and neutralizing antibodies at 1 and 3 months after 3 doses. The study documented that only two-third of SOT recipients developed antibodies, while one-third remained not protected. The study highlights the importance of immune monitoring to optimize vaccination in SOT recipients.

As 30% of SOT recipients does not develop protecting antibodies, several studies evaluated whether a fourth dose was effective in producing protective antibodies. The first study has been made in France and documented an increase of anti-SARS-CoV-2 antibody concentrations after four doses of mRNABNT162b2 vaccine. Similarly, there was an increase of SARS-CoV-2 reactive IFN-gamma producing cells (26).

A different study (27) documented in 71 KTx patients a relevant and protective increase after the fourth dose of mRNA-1273 vaccine in a phase 4 study (NCT04801667).

However, in this study as in another (28), patients with advanced age and with deceased donors may not develop a protective immune response.

Other studies documented the beneficial effect of a fourth vaccine dose. In a case series of 92 KTx recipients (29) reported a significant increase of IgG antibodies against the spike protein.

Benotmane et al (30) documented in 67 KTx recipients that a fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improved serum neutralization against the Delta variant. In a different study, Masset et al (31) highlighted the need of a fourth SARS-CoV-2 mRNA vaccine in strictly seronegative KTx recipients. After the fourth dose, 50% of patients developed protective antibody levels. Factors influencing the positive response were low steroid use, less lymphopenia and a larger time between the third and the fourth dose.

The identification of the Omicron variants changed the picture since now described, due to the number of alterations in the spike glycoproteins that leads to the antibody evasion and to a reduced immune answer to vaccination.

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The study of Iketani et al (32) documented that after two or three doses, the levels of neutralizing antibodies were significantly lower in the case of omicron variants than the levels against delta variant.

The study of Shen (33) collected other studies (34, 35, 36, 37) and documented that after two mRNA vaccine doses, there is minimal antibody-neutralizing level against omicron. Robust neutralization of omicron develops after a third mRNA vaccine dose. The magnitude of omicron neutralization after a third (booster) dose is comparable to the delta neutralization after two doses. A fourth dose (second booster) has the potential to further improving the magnitude and durability of the immune response.

In Israel, Bar On et al (38) selected 1252331 subjects aged 60 years and older. Half of the subjects received three vaccine doses, half four doses. Rates of SARS-CoV-2 infection and severe COVID-19 were lower after a fourth dose of BNT162b2 vaccine than after only three doses.

These data were confirmed by another similar study (39), even if this study highlights a higher protection in persons older than 70 years.

Other studies (40) highlight that the clinical characteristics of the subjects affected by the omicron variant are milder than subjects affected by previous variants. Anyway, a full vaccination is required for an effective protection against the development of a clinical severity.

In the case of transplant patients, several studies (41, 42 , 43) report a suboptimal antibody response against SARS-CoV-2 omicron variants with respect to the wild type (WT) and the delta variant after third dose of mRNA vaccine (figure 4). In a different study (44) a fourth dose of COVID-19 vaccine does dot induce neutralization of the omicron variant among SOT recipients with suboptimal vaccine response.

In conclusion, we may state that:

a) The immune responses to COVID-19 mRNA vaccines include both B and T cells;
b) Immune response in SOT recipients are inferior to those obtained in both healthy controls and SOT candidates;
c) Risk factors for non-response include short duration from TX, treatment for acute rejection, use of Mycophenolate;
d) Natural infection, third and fourth dose improve immune response;
e) Third dose reduces the risk of severe COVID-19
f) Fourth dose may provide protection against the omicron variant
g) Vaccination of all SOT candidates and SOT recipients is a priority.

MONOCLONAL ANTIBODIES

Monoclonal antibodies may be used either for COVID-19 prophylaxis or for the early treatment of COVID-19 infection. We have already described that, despite three or four doses of vaccine, not all patients are protected, in particular patients with a reduced immunocompetence as are transplanted patients.

There are two strategies to protect patients with a weak immune answer to the 3rd dose or with no answer at all.

We may proceed with additional vaccine dose or with the aid of pre-exposition monoclonal antibodies.

REGEN-COV is a combination of two neutralizing monoclonal antibodies, casirivimab and imdevimab, that bind to the receptor-binding domain of the spike protein (45 , 46).

A trial with the use of REGEN-COV given subcutaneously was conducted in 112 sites (47). 1505 participants without any evidence of previous or ongoing infection were assigned to receive REGEN-COV or placebo. At the follow-up, participants who developed symptomatic infection were 7.8% in the placebo group vs. 1.5% in the REGEN-COV group, with a significant difference of $p< 0.001$. This study documented the efficacy and

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safety of REGEN-COV. Almost simultaneously, another study (48) highlighted the efficacy of a different combination of monoclonal antibodies (bamlanivimab-etesevimab) as documented by a study of Dougan et al (49). All these studies were conducted in healthy, not immunocompromised subjects.

After a recommendation of the France Authorities for Health (50), Dimeglio et al (51) gave the possibility to SOT recipients not responders or weak responders to receive casirivimab and indevimab in two distinct doses. Out of 478 patients, 182 received treatment while 296 remained not treated for different reasons. In the follow-up period of 60 days, no SARS-CoV-2 infection verified in the treated group vs. 4.4% infections in the not treated group. In a different study, Ducloux et al (52) obtained similar results with the combination of monoclonal antibodies in KTx recipients. Out of 119 KTx recipients who did not develop protective antibodies after vaccination, 88 were treated versus 31 not treated. No COVID-19 infection developed in monoclonal treated patients vs. 16% infections in not treated patients. The authors conclude that the treatment with monoclonal antibodies confers protection in immunocompromised patients.

This state of art changed with the advent of the Omicron variants.

Kamar et al (53) reported an Omicron breakthrough infection in a KTx patient given pre-exposition casirivimab and imdevimab monoclonal antibodies. The infection occurred despite a high concentration of anti-S antibodies that usually confers a 100% protection against non-Omicron variants. This fact highlights that very high anti-S antibodies are required to prevent Omicron infection. In the study of Planas et al (54), the authors examined the Omicron sensitivity to nine monoclonal antibodies that have been clinically approved or studied in trials (55). The authors found that Omicron was completely or partially resistant to all monoclonal antibodies tested. Previous studies have already documented the Omicron reduced sensitivity to monoclonal antibodies (56, 57). The study of Planas (54) documents a considerable escape of SARS-CoV-2 Omicron to antibody neutralization.

A different approach is the use of a different monoclonal-antibody combination (AZD7442) composed of tixagevimab and cilgavimab. Tixagevimab and cilgavimab bind to distinct epitopes of the SARS-CoV-2 spike protein receptor binding neutralizing the virus (58, 59, 60). In an ongoing phase 3 trial involving 5197 participants randomized to receive either AZD7442 or placebo, the safety and efficacy of AZD7442 was documented in healthy subjects (61) (PROVENT trial, NCT04625725).

The association of tixagevimab and cilgavimab has the name of Evushled. A study from Bertrand et al (62) in KTx recipients compared Evusheld treated patients with vaccinated and protected patients and with patients receiving the association of casirivimab and imdevimab. Patients treated with Evusheld had similar outcomes to vaccinated patients, while patients treated by casirivimab-imdevimab had higher infection rates, principally due to the Omicron variants.

However, another relevant study on prophylaxis induced by Evusheld in KTx recipients (63), documented that less than 10% of patients treated by Evusheld were able to neutralize the Omicron BA.1 variant when given at the dose of 300 mg. Therefore, the Food and Drug Administration (FDA) recommended the revision of the Evusheld dosing (64). Overall, the Omicron variant represents a problem to the use of monoclonal antibodies as prophylactic measure. Indeed, in the study of Iketani (32), BA.2 exhibited marked resistance to 17 neutralizing monoclonal antibodies tested.

Open remains the question if the increased dosage of Evusheld could achieve adequate protection without collateral effects.

A different way to use monoclonal antibodies anti-SARS-CoV-2 is to administer the antibodies not as a prophylaxis, but as an early treatment in patients already affected by COVID-19 infection. A study from Mazzotta et al (65), in line with other previous studies (66, 67), compared the effectiveness of casirivimab/imdevimab with bamlanivimab/etesevimab as an early treatment of no hospitalized patients with COVID-19. A worsening of

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the infection occurred in 6.3% of patients treated with bamlanivimab/etesevimab versus 2% of patients treated with casirivimab/imdevimab with a significant difference. The main limitations of the study were that it was conducted in no immunocompromised patients and in patients not affected by the Omicron variant. Similar limitations are present in the study aimed to evaluate the early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab (68). Sotrovimab, also known as VIR-7831 is an engineered human monoclonal antibody acting against SARS-CoV-2 and other sarbecovirus (69). In a phase 3 study, 583 patients were enrolled in 37 sites and admitted to receive sotrovimab or placebo. All patients had a symptomatic COVID-19 infection and were not affected by the Omicron variant. The effectiveness of sotrovimab was documented by the study that demonstrated a no progression of the disease in the treated group.

In a different study (70), 51 patients with a large prevalence of immunocompromised subjects, were successfully treated by sotrovimab. The median SARS-CoV-2 nucleoprotein (NP) viral load decreased from 7.1-log10 copies/ml before sotrovimab infusion to 5.1 log10 copies/ml 7 days post-infusion. No sotrovimab-resistant spike mutations were detected before infusion, but 53% of these patients had acquired sotrovimab-resistant mutations 7 to 21 days post-treatment. Previously, in vitro studies had shown that sotrovimab could trigger a resistant spike protein due to mutations at positions 340 and 337 (71). All these data claim for a close monitoring of patients treated with monoclonal antibodies for the possibility of the emergence of mutations and resistance to treatment.

A relevant study on the efficacy of monoclonal antibodies in KTx recipients was conducted in France (72). The antibodies (either bamlanivimab alone, or bamlanivimab/etesevimab, or casirivimab + imdevimab) were given to 80 KTx recipients affected by COVID-19 infection and compared to 155 controls. COVID-19 related hospitalization, 30-day admission to intensive care unit (ICU) and 30-day death were the endpoints. The early administration of monoclonal antibodies was beneficial and the overall effects are documented by table 3. These data document the efficacy of monoclonal antibodies given to KTx recipients with a COVID mild form and highlight considering monoclonal antibodies administration for SOT recipients with a weak vaccine response. In addition, the study confirms previous studies (73, 74, 75, 76) who used different associations of monoclonal antibodies.

Table 3 Outcomes at 1 month of kidney transplant recipients treated or not with anti-SARS-CoV-2 monoclonal antibodies.

Outcomes	MoAb group	Control group	*P value*
Severe COVID-19, n (%)	3 (3.8)	30 (19.4)	0.001
Admission to ICU, n (%)	2 (2.5)	24 (15.5)	0.002
Need for mechanical ventilation, n (%)	0 (0.0)	18 (11.6)	<0.001
Death, n (%)	1 (1,25)	18 (11.6)	0.005

Abb. ICU = intensive care unit.

Another study evaluated the association of monoclonal antibodies with remdesivir (RMD) as early treatment in immune compromised patients with unsatisfactory answer to vaccination (77). The conclusion of the study were that the association of RMD and mAbs does not have relevant adverse events, while resulting in good outcomes of the disease.

A more recent study on the effectiveness of early administration of sotrovimab was conducted on 498 high risk, no immunocompromised and immunocompromised patients affected by the B.1.1.529 Omicron variant (78, 79). The study documented the sotrovimab efficacy in preventing hospitalization and mortality both in immunocompromised and no immunocompromised COVID-19 patients affected by the Omicron variant.

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In an interesting study, sotrovimab administration in vaccinated and not vaccinated KTx recipients with SARS-CoV-2 infection due to the Delta and the Omicron BA.1 surges were evaluated (80). Surprisingly, the outcomes were similar, despite Omicron's mildness (81). This fact could be ascribed either to the Omicron immune evasion or to the inadequate immune response of KTx recipients.

In conclusion, according to the data available, the early exposition to monoclonal antibodies documents that the association of casirivimab and imdesimab is effective for the Delta variant. Sotrovimab has no efficacy for the Omicron variants BA.1 and BA.2. The association of Tixagevimab and cilgavimab is under evaluation for the treatment of the Omicron variant BA.2.

DIRECT-ACTING SMALL MOLECULE SARS-CoV-2 ANTIVIRALS

These compounds do not target the variable spike-protein, but target the viral RNA dependent RNA polymerase (RdRp) or the viral main protease (Mpro) (82). We will consider three products: Remdesivir that was the first antiviral approved to treat COVID-19. Molnupivar, inhibitor of the viral RdRp (83). Nirmatrelvir that is an irreversible inhibitor of SARS-CoV-2 Mpro, co-formulated with ritonavir with the name of Paxlovid (84). In vitro and preliminary in vivo studies (82) document that these compounds maintain their activity against all SARS-CoV-2 variants of concerns (VOC), Omicron included.

These findings were confirmed by other studies (85), confirming the effectiveness of antiviral therapies in highly transmittable variants of SARS-CoV-2.

The same antiviral treatments for COVID-19 are recommended by an update on treatment for COVID-19 recently published by British Medical Journal (86).

A wide, recent study (87) confirms on 40776 patients affected by COVID-19, the effectiveness of early molnupivar or nirmatrelvir-ritonavir in hospitalized patients affected by the Omicron variant BA.2. Though this is a retrospective study, according the authors this is the first study who document on a large number of patients the efficacy of the antivirals when given within 2 days of admission to the hospital. An overview of these antiviral molecules is shown in table 4.

Table 4 Overview of SARS-CoV-2 antivirals.

	Nirmatrelvir/Ritonavir (Paxlovid)	Molnupiravir (Lagevrio)	Remdesivir (Veklury)
Population	Age >12 years and >40 kg. Mild to moderate COVID-19 and high risk of progression to hospitalized or death. EMA and FDA approved	Age >18 years. Mild to moderate COVID-19 and high risk of progression or death. EMA and FDA approved	Age >12 years with >40 kg requiring supplemental oxygen. EMA and FDA approved (in and out-of-hospital)
Efficacy (high risk population)	NNT (number needed to treat) = 18 (all cause hospitalization or death)	NNT = 35 (all cause hospitalization or death) when given within the first 5 days of symptom onset	NNT = 22 (all cause hospitalization or death)
Drug interactions	Serious concern (ritonavir strongly inhibits CYP3A4)	Negligible	Monitor when co-administered with strong CYP3A4 inducers/inhibitors
Common side effects	Dysgeusia, diarrhea	Diarrhea, nausea, anemia, mutagenicity?	Bradycardia, drug-induced liver injury, acute kidney injury
Renal/Hepatic impairment	Dose adjustment with moderate renal impairment	No dose adjustment required	Not frecommemded if eGFR<30 mL/min

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Pregnancy	Controindicated	Controindicated	Reassuring data
Activity vs variants	All known variants	All known variants	All known variants

The use of the antivirals in SOT and in particular in KTx recipients faces with two major problems: the efficacy and safety in the immunocompromised host and the interaction with the immunosuppressants.

A study (88) evaluated the early outcomes and the renal function following antiviral treatments after KTx in patients affected by COVID-19. 10 of them received generic antivirals, 8 RDV. 24% of patients had acute kidney injury (AKI) at admission. Upon discharge, more patients treated by RDV had a decrease in the eGFR, but most patients returned to the baseline eGFR within one month from the discharge. Due to the beneficial effects of antivirals, the authors conclude that these drugs appear to be safe, without consequences on the renal function. A different study from Northern Italy (89) evaluated the effect of early RDV administration to prevent severe COVID-19 in SOT recipients. 7 out of 24 patients received pre-emptive RDV with a 3-day course. There was a significant reduced hospitalization rate in outpatient SOT recipients, but a clinical worsening of the already hospitalized SOT recipients. The authors highlight the efficacy of RDV when given as a pre-emptive drug before hospitalization. In a different retrospective cohort study (90), 38 hospitalized KTx recipients received a 5-day RDV treatment versus 127 who received a standard of care treatment. Mortality was significantly reduced (39% vs 83%) and eGFR values improved at discharge.

In a different study (91), Radcliffe et al evaluated the outpatient COVID-19 therapies in SOT recipients during the Omicron surge.

In this study were evaluated 122 patients with SOT and with COVID-19 diagnosed as outpatients. 49 patients received molnupivar and were compared with 24 patients who received the monoclonal antibody sotrovimab as outpatients and with 48 patients who received the standard of care therapy. The results of the study documented that outpatient therapies is important in the management of mild to moderate COVID-19 in SOT recipients. According to the study, patients receiving molnupivar and sotrovimab had reduced hospitalization rate and death also when affected by the Omicron surge.

A similar study evaluated nirmatrelvir/ritonavir, sotrovimab and no SARS-CoV-2 specific treatment (92). The results are similar and claim for the use of SARS-CoV-2 specific agents in the treatment of SOT recipients with COVID-19 infection.

Among the antiviral agents, Remdesivir and Nilmatrelvir/Ritonavir (Paxlovid) seem the most effective, but major problem of RMD is the need of intravenous administration. Major problem with the use of Paxlovid is a severe drug-drug interaction due to the CYP3A inhibition by ritonavir, which can strongly increase the blood concentrations of calcineurin inhibitors (CNIs) (93). Several studies documented the dangerous interaction between Paxlovid and CNIs. A study from Salerno et al (94) documented the risk of supratherapeutic TAC concentrations after restarting with the drugs. According the authors, physicians should carefully re-introduce CNIs after completion of the Paxlovid course. Prikis et al (95) reported a case report of Paxlovid and TAC interaction in a KTx recipient. Wang et al (96) also reported the dangerous interaction between Paxlovid and TAC on four SARS-CoV-2 infected KTx recipients. A recommendation on how to manage the interactions has been published by Lange et al (97). The suggestion of the study is to interrupt CNIs or mammalian target of rapamycin (mTOR) inhibitors during the Paxlovid course and to start again with the immunosuppressants 2-3 days after the end of Paxlovid course. Monitoring drug levels is also highly recommended. Other recommendation is to do not use RMD or Paxlovid with an eGFR less than 30 mL/min.

Paxlovid interacts with several immunosuppressants. A useful guideline on how to manage these drugs is described by the Guidelines by the French Society of Pharmacology and Therapeutics (98), as shown in table 5.

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Table 5 Guidelines by the French Society of Pharmacology and Therapeutics (SFPT).

Immunosuppressive drug	Nature and magnitude of the effect	Therapeutic strategy
Tacrolimus	Increase in tacrolimus exposure by 40 fold	Administer 1/8th of the usual daily dose (DD) on day-1, then stop. Administer 1/2nd of the DD on day-6 then ¾ on day 7 and restart usual DD on day-8. Alternative for low immunological risk: start nirmatrelvir/ritonavir 12h after the last intake of tacrolimus and restart tacrolimus at usual DD 24h after the last antiviral dose. TDM if possible
Cyclosporine	Increase in cyclosporine exposure by 8 fold	Administer 1/5th of the usual DD every day of nirmatrelvir/ritonavir treatment. Administer ½ of the DD on day-6 then ¾ on day-7 and restart usual DD on day-8. TDM if possible
Everolimus/Sirolimus	Increase in everolimus and sirolimus exposure by 15 and 11 fold, respectively	Administer 1/8th of the usual DD on day-1, day-3 and day-5. Usual DD can be restart on day-7. TDM if possible
Mycophenolate mofetil	Weak interaction expected. Possible decrease in mycophenolic acid exposure	The dosage can be maintained

Abbreviation: TDM = Therapeutic dose monitoring.

CONCLUSIONS

The best prophylactic measure is to give all transplant candidates the full cycle of SARS-CoV-2 vaccine before transplant.

A two-dose vaccination is not adequate to protect all SOT recipients and a third or a forth dose is recommended.

To evaluate the level of protection against severe COVID-19, the titer of anti-spike IgG may be useful. The absence of any detectable antibody indicates the lack of effective protection and indicates SOT recipients needing additional protection. Such patients needs an additional booster vaccine dose, possible against the dominant virus variant, which circulates.

It should be avoided the administration of vaccine within the first 3 months after transplantation or in patients recently treated with lymphocyte depleting therapies.

Immunosuppressive drugs limit the immune response after vaccination, but the reduction of the immunosuppressant may cause rejection. However, in SOT recipients with absence of antibodies in response to vaccination, over one year from transplantation and with stable graft function a reduction of the immunosuppressive drugs may be evaluate under strict medical control.

Patients without antibody response after 3-4 doses regimens should be treated with prophylaxis with monoclonal antibodies. Caveat to the risk of potential resistances of new variants against the administered antibodies.

Antiviral molecules may be administered to patients with COVID-19 infection with concern to drug-drug interferences with immunosuppressive drugs.

RMD should not be administered to patients with eGFR less than 30/mL/min.

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REFERENCES

1) Fishman JA. The Immunocompromised Transplant Recipient and SARS-CoV-2 Infection. *J Am Soc Nephrol*. **2020**; *31*:1147-1149.
2) Fishman JA, Roberts MB, Zhang EW, Kumar D, Hirsch HH, Maggiore U. Case 29-**2020**: A 66-Year-Old Man with Fever and Shortness of Breath after Liver Transplantation. *N Engl J Med.* **2020;** 17; *383*:1168-1180.
3) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* **2020**; *383*: 2603-2615.
4) Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* **2021**; *384*: 403-416.
5) Hamm SR, Møller DL, Pérez-Alós L, Hansen CB, Pries-Heje MM, Heftdal LD, Hasselbalch RB, Fogh K, Madsen JR, Almagro Armenteros JJ, Knudsen AD, Poulsen JR, Frikke-Schmidt R, Hilsted LM, Sørensen E, Ostrowski SR, Harboe ZB, Perch M, Sørensen SS, Rasmussen A, Bundgaard H, Garred P, Iversen K, Nielsen SD. Decline in Antibody Concentration 6 Months After Two Doses of SARS-CoV-2 BNT162b2 Vaccine in Solid Organ Transplant Recipients and Healthy Controls. *Front Immunol.* **2022**;*13*: 832501. eCollection 2022.
6) Verleye A, Wijtvliet V, Abrams S, Hellemans R, Bougrea R, Massart A, Pipeleers L, Wissing KM, Ariën KK, De Winter BY, Van Damme P, Abramowicz D, Ledeganck KJ. Seroconversion rate after primary vaccination with two doses of BNT162b2 versus mRNA-1273 in solid organ transplant recipients: a systematic review and meta-analysis. *Nephrol Dial Transplant.* **2022**; *37*: 1566-1575.
7) Liefeldt L, Glander P, Klotsche J, Straub-Hohenbleicher H, Budde K, Eberspächer B, Friedersdorff F, Halleck F, Hambach P, Hofmann J, Koch N, Schmidt D, Schrezenmeier E, Seelow E, Weber U, Zukunft B, Eckardt KU, Choi M, Bachmann F, Waiser J. Predictors of Serological Response to SARS-CoV-2 Vaccination in Kidney Transplant Patients: Baseline Characteristics, Immunosuppression, and the Role of IMPDH Monitoring. *J Clin Med.* **2022**; *11*:1697.
8) Balsby D, Nilsson AC, Möller S, Lindvig SO, Davidsen JR, Abazi R, Poulsen MK, Holden IK, Justesen US, Bistrup C, Johansen IS. Determinants of Antibody Response to a Third SARS-CoV-2 mRNA Vaccine Dose in Solid Organ Transplant Recipients: Results from the Prospective Cohort Study COVAC-Tx. *Vaccines (Basel).* **2022**; *10*: 565.
9) Hod T, Ben-David A, Olmer L, Scott N, Ghinea R, Mor E, Levy I, Indenbaum V, Lustig Y, Grossman E, Rahav G. BNT162b2 Third Booster Dose Significantly Increases the Humoral Response Assessed by Both RBD IgG and Neutralizing Antibodies in Renal Transplant Recipients. *Transpl Int.* **2022**; *35*:10239.
10) Manothummetha K, Chuleerarux N, Sanguankeo A, Kates OS, Hirankarn N, Thongkam A, Dioverti-Prono MV, Torvorapanit P, Langsiri N, Worasilchai N, Moonla C, Plongla R, Garneau WM, Chindamporn A, Nissaisorakarn P, Thaniyavarn T, Nematollahi S, Permpalung N. Immunogenicity and Risk Factors Associated With Poor Humoral Immune Response of SARS-CoV-2 Vaccines in Recipients of Solid Organ Transplant: A Systematic Review and Meta-Analysis. *JAMA Netw Open.* **2022** ; *5*: e226822.
11) Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, Martzloff J, Perrin P, Moulin B, Fafi-Kremer S, Caillard S. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int.* **2021**; *99*:1498-1500.
12) Meyer M, Constancias F, Worth C, Meyer A, Muller M, Boussuge A, Kaltenbach G, Schmitt E, Chayer S, Velay A, Vogel T, Fafi-Kremer S, Karcher P. Humoral immune response after COVID-19 infection or BNT162b2 vaccine among older adults: evolution over time and protective thresholds. *Geroscience.* **2022**; *44*:1229-1240.
13) Mazzoni A, Vanni A, Spinicci M, Lamacchia G, Kiros ST, Rocca A, Capone M, Di Lauria N, Salvati L, Carnasciali A, Mantengoli E, Farahvachi P, Zammarchi L, Lagi F, Colao MG, Liotta F, Cosmi L, Maggi L, Bartoloni A, Rossolini GM, Annunziato F. SARS-CoV-2 infection and vaccination trigger long-lived B and CD4+ T lymphocytes with implications for booster strategies. *J Clin Invest.* **2022** ; *132*: e157990.
14) Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A, Nakao C, Rayaprolu V, Rawlings SA, Peters B, Krammer F, Simon V, Saphire EO, Smith DM, Weiskopf D, Sette A, Crotty S. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science.* **2021** ; *371*: eabf4063.
15) Mazzoni A, Di Lauria N, Maggi L, Salvati L, Vanni A, Capone M, Lamacchia G, Mantengoli E, Spinicci M, Zammarchi L, Kiros ST, Rocca A, Lagi F, Colao MG, Parronchi P, Scaletti C, Turco L, Liotta F, Rossolini GM, Cosmi L, Bartoloni A, Annunziato F;

COVID-19 Research Group. First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in subjects who have recovered from COVID-19. *J Clin Invest.* **2021**; *131*: e149150

16) Mazzoni A, Maggi L, Capone M, Spinicci M, Salvati L, Colao MG, Vanni A, Kiros ST, Mencarini J, Zammarchi L, Mantengoli E, Menicacci L, Caldini E, Romagnani S, Liotta F, Morettini A, Rossolini GM, Bartoloni A, Cosmi L, Annunziato F. Cell-mediated and humoral adaptive immune responses to SARS-CoV-2 are lower in asymptomatic than symptomatic COVID-19 patients. *Eur J Immunol.* **2020** ; *50*: 2013-2024.
17) Mazzoni A, Maggi L, Capone M, Vanni A, Spinicci M, Salvati L, Tekle Kiros S, Semeraro R, Pengue L, Colao MG, Magi A, Rossolini GM, Liotta F, Cosmi L, Bartoloni A, Annunziato F. Heterogeneous magnitude of immunological memory to SARS-CoV-2 in recovered individuals. *Clin Transl Immunology.* **2021**;*10*: e1281
18) Buehrle DJ, Sutton RR, McCann EL, Lucas AE. A Review of Treatment and Prevention of Coronavirus Disease 2019 among Solid Organ Transplant Recipients. *Viruses.* **2021** ; *13*:1706.
19) Dęborska-Materkowska D, Kamińska D. The Immunology of SARS-CoV-2 Infection and Vaccines in Solid Organ Transplant Recipients. *Viruses.* **2021**;*13*:1879.
20) Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, Tau N, Mashraki T, Nesher E, Rahamimov R. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect.* **2021** ; *27*: 1173.e1-1173.e4.
21) Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, Hebral AL, Izopet J, Kamar N. Safety and Immunogenicity of Anti-SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants. *Ann Intern Med.* **2021**; *174*:1336-1338.
22) Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA.* **2021**; *325*: 2204-2206.
23) Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, Selzner N, Schiff J, McDonald M, Tomlinson G, Kulasingam V, Kumar D, Humar A. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. *N Engl J Med.* **2021**; *385*:1244-1246.
24) Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N Engl J Med.* **2021**; *385*: 661-662.
25) Kamar N, Abravanel F, Marion O, Esposito L, Hebral AL, Médrano C, Guitard J, Lavayssière L, Cointault O, Nogier MB, Bellière J, Faguer S, Couat C, Del Bello A, Izopet J. Anti-SARS-CoV-2 spike protein and neutralizing antibodies at 1 and 3 months after three doses of SARS-CoV-2 vaccine in a large cohort of solid organ transplant patients. *Am J Transplant.* **2022**; *22*:1467-1474.
26) Kamar N, Abravanel F, Marion O, Romieu-Mourez R, Couat C, Del Bello A, Izopet J. Assessment of 4 Doses of SARS-CoV-2 Messenger RNA-Based Vaccine in Recipients of a Solid Organ Transplant. *JAMA Netw Open.* **2021**; *4*: e2136030.
27) Cristelli MP, Nakamura MR, Viana LA, Tedesco-Silva H, Medina-Pestana J. The Fourth Dose of CoronaVac Vaccine Results in a Small Increase of Seroconversion and Antibody Values Among Kidney Transplant Recipients. *Transplantation.* **2022** . Online ahead of print.
28) Mitchell J, Kim J, Alejo JL, Chiang TP, Karaba AH, Blankson JN, Aytenfisu TY, Chang A, Abedon AT, Avery RK, Tobian AA, Massie AB, Levan ML, Warren DS, Garonzik-Wang JM, Segev DL, Werbel WA. Antibody Response to a Fourth Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: An Update.*Transplantation.* **2022**; *106* : e338-e340.
29) Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody Response to a Fourth Messenger RNA COVID-19 Vaccine Dose in Kidney Transplant Recipients: A Case Series. *Ann Intern Med.* **2022**; *175*: 455-456.
30) Benotmane I, Bruel T, Planas D, Fafi-Kremer S, Schwartz O, Caillard S. A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the Delta variant in kidney transplant recipients. *Kidney Int.* **2022** ; *101*:1073-1076.
31) Masset C, Benotmane I, Dantal J, Garandeau C, Gauthier-Vargas G, Cantarovich D, Meurette A, Giral M, Caillard S, Blancho G. A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients. *Kidney Int.* **2022** ; *10*: 825-826.
32) Iketani S, Liu L, Guo Y, Liu L, Chan JF, Huang Y, Wang M, Luo Y, Yu J, Chu H, Chik KK, Yuen TT, Yin MT, Sobieszczyk ME, Huang Y, Yuen KY, Wang HH, Sheng Z, Ho DD. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature.* **2022**; 604: 553-556.
33) Shen X. Boosting immunity to Omicron. *Nat Med.* **2022**; *28*: 445-446.
34) Pérez-Then E, Lucas C, Monteiro VS, Miric M, Brache V, Cochon L, Vogels CBF, Malik AA, De la Cruz E, Jorge A, De Los Santos M, Leon P, Breban MI, Billig K, Yildirim I, Pearson C, Downing R, Gagnon E, Muyombwe A, Razeq J, Campbell M, Ko AI, Omer SB, Grubaugh ND, Vermund SH, Iwasaki A. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. *Nat Med.* **2022**; *28*: 481-485.
35) Cheng SMS, Mok CKP, Leung YWY, Ng SS, Chan KCK, Ko FW, Chen C, Yiu K, Lam BHS, Lau EHY, Chan KKP, Luk LLH, Li JKC, Tsang LCH, Poon LLM, Hui DSC, Peiris M. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med.* **2022**; *28*: 486-489.
36) Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Schommers P, Lehmann C, Kurth F, Sander LE, Klein F. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. *Nat Med.* **2022**; *28*: 477-480.
37) VanBlargan LA, Errico JM, Halfmann PJ, Zost SJ, Crowe JE Jr, Purcell LA, Kawaoka Y, Corti D, Fremont DH, Diamond MS. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Nat Med.* **2022**; *28*: 490-495.
38) Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, Alroy-Preis S, Ash N, Huppert A, Milo R. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. *N Engl J Med.* **2022**; *386*: 1712-1720.

39) Wohl A, Leibowitz R. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. *N Engl J Med.* **2022**; *386*: 2441
40) Zhang J, Chen N, Zhao D, Zhang J, Hu Z, Tao Z. Clinical Characteristics of COVID-19 Patients Infected by the Omicron Variant of SARS-CoV-2. *Front Med (Lausanne).* **2022** ; *9*: 912367.
41) Al Jurdi A, Gassen RB, Borges TJ, Lape IT, Morena L, Efe O, Solhjou Z, El Fekih R, Deban C, Bohan B, Pattanayak V, Kotton CN, Azzi JR, Riella LV. Suboptimal antibody response against SARS-CoV-2 Omicron variant after third dose of mRNA vaccine in kidney transplant recipients. *Kidney Int.* **2022**; *101*: 1282-1286.
42) Dejnirattisai W, Shaw RH, Supasa P, Liu C, Stuart AS, Pollard AJ, Liu X, Lambe T, Crook D, Stuart DI, Mongkolsapaya J, Nguyen-Van-Tam JS, Snape MD, Screaton GR; Com-COV2 study group. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. *Lancet.* **2022**; *399*: 234-236.
43) Karaba AH, Zhu X, Liang T, Wang KH, Rittenhouse AG, Akinde O, Eby Y, Ruff JE, Blankson JN, Abedon AT, Alejo JL, Cox AL, Bailey JR, Thompson EA, Klein SL, Warren DS, Garonzik-Wang JM, Boyarsky BJ, Sitaras I, Pekosz A, Segev DL, Tobian AAR, Werbel WA. A third dose of SARS-CoV-2 vaccine increases neutralizing antibodies against variants of concern in solid organ transplant recipients. *Am J Transplant.* **2022**; *22*:1253-1260.
44) Karaba AH, Johnston TS, Aytenfisu TY, Akinde O, Eby Y, Ruff JE, Abedon AT, Alejo JL, Blankson JN, Cox AL, Bailey JR, Klein SL, Pekosz A, Segev DL, Tobian AAR, Werbel WA. A Fourth Dose of COVID-19 Vaccine Does Not Induce Neutralization of the Omicron Variant Among Solid Organ Transplant Recipients With Suboptimal Vaccine Response. *Transplantation.* **2022**; 106: 1440-1444.
45) Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, Giordano S, Lanza K, Negron N, Ni M, Wei Y, Atwal GS, Murphy AJ, Stahl N, Yancopoulos GD, Kyratsous CA. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science.* **2020**; *369*: 1014-1018.
46) Copin R, Baum A, Wloga E, Pascal KE, Giordano S, Fulton BO, Zhou A, Negron N, Lanza K, Chan N, Coppola A, Chiu J, Ni M, Wei Y, Atwal GS, Hernandez AR, Saotome K, Zhou Y, Franklin MC, Hooper AT, McCarthy S, Hamon S, Hamilton JD, Staples HM, Alfson K, Carrion R Jr, Ali S, Norton T, Somersan-Karakaya S, Sivapalasingam S, Herman GA, Weinreich DM, Lipsich L, Stahl N, Murphy AJ, Yancopoulos GD, Kyratsous CA. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. *Cell.* **2021**;*184*: 3949-3961
47) O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, Bar KJ, Barnabas RV, Barouch DH, Cohen MS, Hurt CB, Burwen DR, Marovich MA, Hou P, Heirman I, Davis JD, Turner KC, Ramesh D, Mahmood A, Hooper AT, Hamilton JD, Kim Y, Purcell LA, Baum A, Kyratsous CA, Krainson J, Perez-Perez R, Mohseni R, Kowal B, DiCioccio AT, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Weinreich DM; Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med.* **2021** ; *385*: 1184-1195.
48) Merison T, Goldman A, Bomze D. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med.* **2021**; *385*: e70.
49) Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, Morris J, Crystal C, Igbinadolor A, Huhn G, Cardona J, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Dabora MC, Klekotka P, Shen L, Skovronsky DM; BLAZE-1 Investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med.* **2021** ; *385*: 1382-1392.
50) National French Health Authority. RONAPREVE (casirivimab-imdevimab) (prophylaxie pré-exposition de l'infection à SARS-CoV-2). Available at https://www.has-sante.fr/jcms/p_3281544/fr/ronapreve-casirivimab-imdevimab-prophylaxie-pre-expositionj-de-l-infection a- sars-cov-2. Accessed August 6, 2022
51) Dimeglio C, Del Bello A, Chapuy-Regaud S, Esposito L, Danet C, Couat C, Izopet J, Kamar N. Casirivimab-imdevimab to Prevent SARS-CoV-2 Infections in Solid Organ Transplant Recipients. *Transplantation.* **2022**; *106*: e275-e276.
52) Ducloux D, Courivaud C. REGEN-Cov antibody combination to prevent COVID-19 infection in kidney transplant recipient without detectable antibody response to optimal vaccine scheme. *Kidney Int.* **2022**; *101*: 645-646.
53) Kamar N, Gouin A, Izopet J. Omicron breakthrough infection in a kidney-transplant patient given pre-exposition casirivimab and imdevimab monoclonal antibodies. *Transpl Infect Dis.* **2022**; *24*: e13803
54) Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, Bolland WH, Porrot F, Staropoli I, Lemoine F, Péré H, Veyer D, Puech J, Rodary J, Baele G, Dellicour S, Raymenants J, Gorissen S, Geenen C, Vanmechelen B, Wawina-Bokalanga T, Martí-Carreras J, Cuypers L, Sève A, Hocqueloux L, Prazuck T, Rey FA, Simon-Loriere E, Bruel T, Mouquet H, André E, Schwartz O. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature.* **2022**; *602*: 671-675
55) Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol.* **2021**; *21*: 382-393
56) Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, Huang W, Li Q, Wang P, An R, Wang J, Wang Y, Niu X, Yang S, Liang H, Sun H, Li T, Yu Y, Cui Q, Liu S, Yang X, Du S, Zhang Z, Hao X, Shao F, Jin R, Wang X, Xiao J, Wang Y, Xie XS. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature.* **2022**; *602*: 657-663.
57) Cameroni E, Bowen JE, Rosen LE, Saliba C, Zepeda SK, Culap K, Pinto D, VanBlargan LA, De Marco A, di Iulio J, Zatta F, Kaiser H, Noack J, Farhat N, Czudnochowski N, Havenar-Daughton C, Sprouse KR, Dillen JR, Powell AE, Chen A, Maher C, Yin L, Sun D, Soriaga L, Bassi J, Silacci-Fregni C, Gustafsson C, Franko NM, Logue J, Iqbal NT, Mazzitelli I, Geffner J, Grifantini R, Chu H, Gori A, Riva A, Giannini O, Ceschi A, Ferrari P, Cippà PE, Franzetti-Pellanda A, Garzoni C, Halfmann PJ, Kawaoka Y, Hebner C, Purcell LA, Piccoli L, Pizzuto MS, Walls AC, Diamond MS, Telenti A, Virgin HW, Lanzavecchia A, Snell G, Veesler D, Corti D. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature.* **2022**; *602*: 664-670.

58) Loo YM, McTamney PM, Arends RH, Abram ME, Aksyuk AA, Diallo S, Flores DJ, Kelly EJ, Ren K, Roque R, Rosenthal K, Streicher K, Tuffy KM, Bond NJ, Cornwell O, Bouquet J, Cheng LI, Dunyak J, Huang Y, Rosenbaum AI, Pilla Reddy V, Andersen H, Carnahan RH, Crowe JE Jr, Kuehne AI, Herbert AS, Dye JM, Bright H, Kallewaard NL, Pangalos MN, Esser MT. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. *Sci Transl Med.* **2022**;*14*: eabl8124

59) Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schäfer A, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Martinez DR, Williamson LE, Chen EC, Jones T, Day S, Myers L, Hassan AO, Kafai NM, Winkler ES, Fox JM, Shrihari S, Mueller BK, Meiler J, Chandrashekar A, Mercado NB, Steinhardt JJ, Ren K, Loo YM, Kallewaard NL, McCune BT, Keeler SP, Holtzman MJ, Barouch DH, Gralinski LE, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE Jr. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature.* **2020**; *584*: 443-449.

60) Dong J, Zost SJ, Greaney AJ, Starr TN, Dingens AS, Chen EC, Chen RE, Case JB, Sutton RE, Gilchuk P, Rodriguez J, Armstrong E, Gainza C, Nargi RS, Binshtein E, Xie X, Zhang X, Shi PY, Logue J, Weston S, McGrath ME, Frieman MB, Brady T, Tuffy KM, Bright H, Loo YM, McTamney PM, Esser MT, Carnahan RH, Diamond MS, Bloom JD, Crowe JE Jr. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. *Nat Microbiol.* **2021**; *6*: 1233-1244.

61) Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, Ambery P, Arends RH, Beavon R, Dey K, Garbes P, Kelly EJ, Koh GCKW, Near KA, Padilla KW, Psachoulia K, Sharbaugh A, Streicher K, Pangalos MN, Esser MT; PROVENT Study Group. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. *N Engl J Med.* **2022**; *386*: 2188-2200.

62) Bertrand D, Laurent C, Lemée V, Lebourg L, Hanoy M, Le Roy F, Nezam D, Pruteanu D, Grange S, de Nattes T, Lemoine M, Candon S, Guerrot D. Efficacy of anti-SARS-CoV-2 monoclonal antibody prophylaxis and vaccination on the Omicron variant of COVID-19 in kidney transplant recipients. *Kidney Int.* **2022** ; *102*: 440-442.

63) Benotmane I, Velay A, Gautier-Vargas G, Olagne J, Thaunat O, Fafi-Kremer S, Caillard S. Pre-exposure prophylaxis with 300 mg Evusheld elicits limited neutralizing activity against the Omicron variant. *Kidney Int.* **2022**; *102*: 442-444.

64) US Food & Drug Administration. FDA authorizes revisions to Evusheld dosing. Accessed May 24 2002. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing

65) Mazzotta V, Cozzi-Lepri A, Colavita F, Lanini S, Rosati S, Lalle E, Mastrorosa I, Cimaglia C, Vergori A, Bevilacqua N, Lapa D, Mariano A, Bettini A, Agrati C, Piselli P, Girardi E, Castilletti C, Garbuglia AR, Vaia F, Nicastri E, Antinori A. Emulation of a Target Trial From Observational Data to Compare Effectiveness of Casirivimab/Imdevimab and Bamlanivimab/Etesevimab for Early Treatment of Non-Hospitalized Patients With COVID-19. *Front Immunol.* **2022**; *13*: 868020.

66) Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* **2021**; *325*: 632-644.

67) Dougan M, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, Morris J, Crystal C, Igbinadolor A, Huhn G, Cardona J, Shawa I, Kumar P, Blomkalns A, Adams AC, Van Naarden J, Custer KL, Knorr J, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Sabo J, Patel DR, Dabora MC, Williams M, Klekotka P, Shen L, Skovronsky DM, Nirula A. A Randomized, Placebo-Controlled Clinical Trial of Bamlanivimab and Etesevimab Together in High-Risk Ambulatory Patients With COVID-19 and Validation of the Prognostic Value of Persistently High Viral Load. *Clin Infect Dis.* **2022**; 75: e440-e449

68) Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL, Hebner CM, Sager J, Mogalian E, Tipple C, Peppercorn A, Alexander E, Pang PS, Free A, Brinson C, Aldinger M, Shapiro AE; COMET-ICE Investigators. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med.* **2021**; *385*:1941-1950.

69) Pinto D, Park YJ, Beltramello M, Walls AC, Tortorici MA, Bianchi S, Jaconi S, Culap K, Zatta F, De Marco A, Peter A, Guarino B, Spreafico R, Cameroni E, Case JB, Chen RE, Havenar-Daughton C, Snell G, Telenti A, Virgin HW, Lanzavecchia A, Diamond MS, Fink K, Veesler D, Corti D. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature.* **2020**; *583*: 290-295

70) Vellas C, Trémeaux P, Del Bello A, Latour J, Jeanne N, Ranger N, Danet C, Martin-Blondel G, Delobel P, Kamar N, Izopet J. Resistance mutations in SARS-CoV-2 omicron variant in patients treated with sotrovimab. *Clin Microbiol Infect.* **2022** : *S1198-*743X(22)00258-0.

71) Rockett R, Basile K, Maddocks S, Fong W, Agius JE, Johnson-Mackinnon J, Arnott A, Chandra S, Gall M, Draper J, Martinez E, Sim EM, Lee C, Ngo C, Ramsperger M, Ginn AN, Wang Q, Fennell M, Ko D, Lim HL, Gilroy N, O'Sullivan MVN, Chen SC, Kok J, Dwyer DE, Sintchenko V. Resistance Mutations in SARS-CoV-2 Delta Variant after Sotrovimab Use. *N Engl J Med.* **2022**; *386*: 1477-1479.

72) Gueguen J, Colosio C, Del Bello A, Scemla A, N'Guyen Y, Rouzaud C, Carvalho-Schneider C, Gautier Vargas G, Tremolières P, Eddine AJ, Masset C, Thaunat O, Chabannes M, Malvezzi P, Pommerolle P, Couzi L, Kamar N, Caillard S, Gatault P. Early Administration of Anti-SARS-CoV-2 Monoclonal Antibodies Prevents Severe COVID-19 in Kidney Transplant Patients. *Kidney Int Rep.* **2022**; *7*:1241-1247.

73) Dhand A, Lobo SA, Wolfe K, Feola N, Lee L, Nog R, Chen D, Glicklich D, Diflo T, Nabors C. Casirivimab-imdevimab for Treatment of COVID-19 in Solid Organ Transplant Recipients: An Early Experience. *Transplantation.* **2021**; *105*: e68-e69.

74) Dhand A, Lobo SA, Wolfe K, Feola N, Nabors C. Bamlanivimab for treatment of COVID-19 in solid organ transplant recipients: Early single-center experience. *Clin Transplant.* **2021**; *35*: e14245.
75) Kutzler HL, Kuzaro HA, Serrano OK, Feingold A, Morgan G, Cheema F. Initial experience of bamlanivimab monotherapy use in solid organ transplant recipients. *Transpl Infect Dis.* **2021**; *23*: e13662.
76) Vellas C, Del Bello A, Debard A, Steinmeyer Z, Tribaudeau L, Ranger N, Jeanne N, Martin-Blondel G, Delobel P, Kamar N, Izopet J. Influence of treatment with neutralizing monoclonal antibodies on the SARS-CoV-2 nasopharyngeal load and quasispecies. *Clin Microbiol Infect.* **2022**; *28*: 139.e5-139.e8.
77) Biscarini S, Villa S, Genovese C, Tomasello M, Tonizzo A, Fava M, Iannotti N, Bolis M, Mariani B, Valzano AG, Morlacchi LC, Donato F, Castellano G, Cassin R, Carrabba M, Muscatello A, Gori A, Bandera A, Lombardi A. Safety Profile and Outcomes of Early COVID-19 Treatments in Immunocompromised Patients: A Single-Centre Cohort Study. *Biomedicines*. **2022** ; *10*: 2002.
78) Birk NK, Jain S, Massoud L, Ramesh D, Monday L, Muma B, Williams J, Alangaden G, Ramesh M. Real-world Experience of Sotrovimab in High-risk, Immunocompromised COVID-19 Patients. *Open Forum Infect Dis.* **2022** ; *9*: ofac282.
79) Centers for Disease Control and Prevention. COVID data trecker. **2022**. Available at: https://covid.cdc.gov/covid-data-tracker. Accessed 21 July 2022
80) Vathsala A, Somani J, Ross D'Costa M, Lum L, Wong ET, Sran HK. Comparative outcomes after early Sotrovimab administration in vaccinated and unvaccinated kidney transplant recipients with SARS-CoV-2 infection during the Delta and Omicron BA.1 surges. *Transpl Infect Dis.* **2022**: e13930.
81) Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, Ghamande S, Douin DJ, Talbot HK, Casey JD, Mohr NM, Zepeski A, Shapiro NI, Gibbs KW, Files DC, Hager DN, Shehu A, Prekker ME, Erickson HL, Exline MC, Gong MN, Mohamed A, Johnson NJ, Srinivasan V, Steingrub JS, Peltan ID, Brown SM, Martin ET, Monto AS, Khan A, Hough CL, Busse LW, Ten Lohuis CC, Duggal A, Wilson JG, Gordon AJ, Qadir N, Chang SY, Mallow C, Rivas C, Babcock HM, Kwon JH, Halasa N, Grijalva CG, Rice TW, Stubblefield WB, Baughman A, Womack KN, Rhoads JP, Lindsell CJ, Hart KW, Zhu Y, Adams K, Schrag SJ, Olson SM, Kobayashi M, Verani JR, Patel MM, Self WH; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Clinical severity of , and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ.* **2022**; *376*: e069761
82) Vangeel L, Chiu W, De Jonghe S, Maes P, Slechten B, Raymenants J, André E, Leyssen P, Neyts J, Jochmans D. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res.* **2022**;*198*: 105252.
83) Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, Morin MJ, Szewczyk LJ, Painter GR. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. *Antimicrob Agents Chemother.* **2021** ; *65*: e02428-20.
84) Owen DR, Allerton CMN, Anderson AS, Aschenbrenner L, Avery M, Berritt S, Boras B, Cardin RD, Carlo A, Coffman KJ, Dantonio A, Di L, Eng H, Ferre R, Gajiwala KS, Gibson SA, Greasley SE, Hurst BL, Kadar EP, Kalgutkar AS, Lee JC, Lee J, Liu W, Mason SW, Noell S, Novak JJ, Obach RS, Ogilvie K, Patel NC, Pettersson M, Rai DK, Reese MR, Sammons MF, Sathish JG, Singh RSP, Steppan CM, Stewart AE, Tuttle JB, Updyke L, Verhoest PR, Wei L, Yang Q, Zhu Y. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science.* **2021**; *374*: 1586-1593.
85) Schöning V, Kern C, Chaccour C, Hammann F. Effectiveness of Antiviral Therapy in Highly-Transmissible Variants of SARS-CoV-2: A Modeling and Simulation Study. *Front Pharmacol.* **2022**;*13*: 816429
86) Update to living WHO guideline on drugs for covid-19 *BMJ* **2022**; *378*: o1713.
87) Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. *Lancet Infect Dis*. **2022**: *S1473*-3099(22)00507-2.
88) Elec AD, Oltean M, Goldis P, Cismaru C, Lupse M, Muntean A, Elec FI. COVID-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment. *Int J Infect Dis.* **2021**; *104*: 426-432
89) Colaneri M, Amarasinghe N, Rezzonico L, Pieri TC, Segalini E, Sambo M, Roda S, Meloni F, Gregorini M, Rampino T, Pelenghi S, Ricciardi A, Bruno R. Early remdesivir to prevent severe COVID-19 in recipients of solid organ transplant: a real-life study from Northern Italy. *Int J Infect Dis.* **2022**;*121*:157-160
90) Elec F, Magnusson J, Elec A, Muntean A, Antal O, Moisoiu T, Cismaru C, Lupse M, Oltean M. COVID-19 and kidney transplantation: the impact of remdesivir on renal function and outcome - a retrospective cohort study. *Int J Infect Dis.* **2022**; *118*: 247-253.
91) Radcliffe C, Palacios CF, Azar MM, Cohen E, Malinis M. Real-world experience with available, outpatient COVID-19 therapies in solid organ transplant recipients during the omicron surge. *Am J Transplant.* **2022**: Online ahead of print.
92) Hedvat J, Lange NW, Salerno DM, DeFilippis EM, Kovac D, Corbo H, Chen JK, Choe JY, Lee JH, Anamisis A, Jennings DL, Codispodo G, Shertel T, Brown RS Jr, Pereira MR. COVID-19 therapeutics and outcomes among solid organ transplant recipients during the Omicron BA.1 era. *Am J Transplant.* **2022**: Online ahead of print.
93) Gandolfini I, Crespo M, Hellemans R, Maggiore U, Mariat C, Mjoen G, Oniscu GC, Peruzzi L, Sever MS, Watschinger B, Hilbrands L. Issues regarding COVID-19 in kidney transplantation in the era of the omicron variant: a commentary by the era descartes working group. *Nephrol Dial Transplant.* **2022**: gfac203.

94) Salerno DM, Jennings DL, Lange NW, Kovac DB, Shertel T, Chen JK, Hedvat J, Scheffert J, Brown RS Jr, Pereira MR. Early clinical experience with nirmatrelvir/ritonavir for the treatment of COVID-19 in solid organ transplant recipients. *Am J Transplant.* **2022**; *22*: 2083-2088.
95) Prikis M, Cameron A. Paxlovid (Nirmatelvir/Ritonavir) and Tacrolimus Drug-Drug Interaction in a Kidney Transplant Patient with SARS-2-CoV infection: A Case Report. *Transplant Proc.* **2022**: S0041
96) Wang AX, Koff A, Hao D, Tuznik NM, Huang Y. Effect of nirmatrelvir/ritonavir on calcineurin inhibitor levels: Early experience in four SARS-CoV-2 infected kidney transplant recipients. *Am J Transplant.* **2022**; *22*: 2117-2119.
97) Lange NW, Salerno DM, Jennings DL, Choe J, Hedvat J, Kovac DB, Scheffert J, Shertel T, Ratner LE, Brown RS Jr, Pereira MR. Nirmatrelvir/ritonavir use: Managing clinically significant drug-drug interactions with transplant immunosuppressants. *Am J Transplant.* **2022**; *22*: 1925-1926.
98) Lemaitre F, Grégoire M, Monchaud C, Bouchet S, Saint-Salvi B, Polard E; SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT); French Pharmacovigilance Network (CRPV); ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group; SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT); French Pharmacovigilance Network (CRPV); ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group. Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT). *Therapie.* **2022**: S0040-5957(22)00065-8.