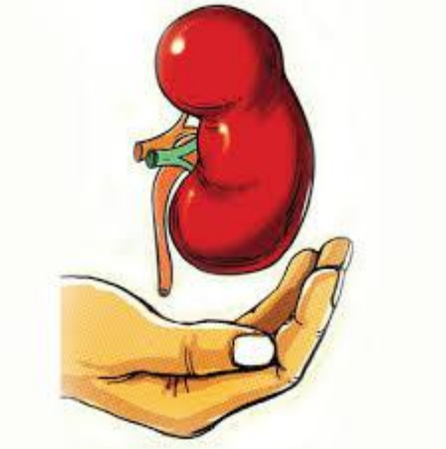
# Transplant Pharmacotherapy Considerations in Patients with COVID-19



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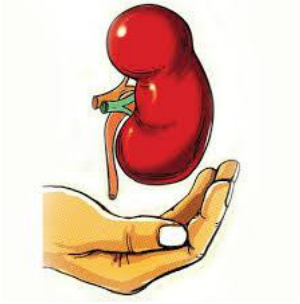
# People at high risk for severe COVID 19:

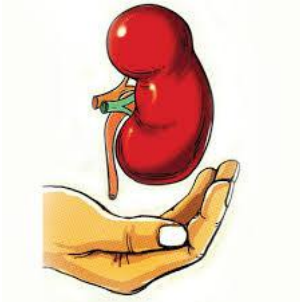


**Immuno-compromised patients:**

- Patient who receive chemotherapy,
- Immunosuppressive drug due to organ transplantation,
- Active cancer,
- Prednisolone with the dose of >12.5mg/day for more than 2 weeks.

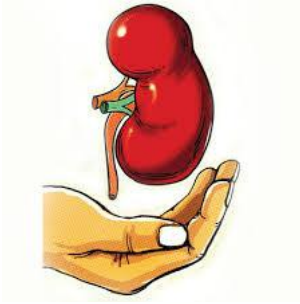
**Patients with these past medical histories:**

- Hypertension,
- Chronic kidney disease,
- Cardio-vascular disorders,
- Uncontrolled Diabetes (HbA1C>7.5)
- Chronic respiratory disorders,
- BMI>40.



# COVID-19 antiviral pharmacotherapy considerations in organ transplant patients

# Recipients who will be managed as out-patient:



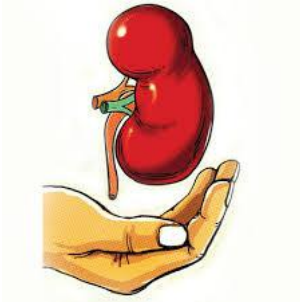
- These are patients with high clinical suspicion of COVID-19 or confirmed cases of infection but without hospitalization indications ( without respiratory distress, O2 sat>93%, RR<24) with normal Lung CT-scan/CXR.
- Recommended antiviral regimen:

Tab Hydroxychloquin 400mg stat, then 200 g every 12hours for 5-10 days.

OR

Tab Hydroxychloquin 500mg stat, then 250 g every 12hours for 5-10 days.

# Recipients who will be hospitalized:

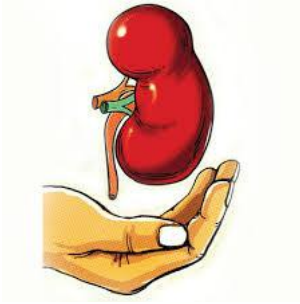


- These are patients with respiratory distress ± O2 sat>93% ± RR<24)

- Recommended antiviral regimen (dual therapy):

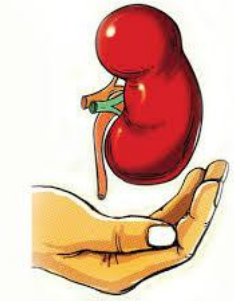
1. Tab Hydroxychloquin 400mg stat, then 200 g every 12hours for 7-10 days.
   OR
   Tab Hydroxychloquin 500mg stat, then 250 g every 12hours for 7-10 days.

2. Tab Lopinavir/Ritonavir 200/50 mg, 2 tablet, every 12 hours, for 7-14 days.
   OR
   Tab Atazanavir/Ritonavir 200/300 mg, 1 tablet, every 12 hours, for 7-14 days.



# Immuno-suppression management in organ transplant patients with COVID-19

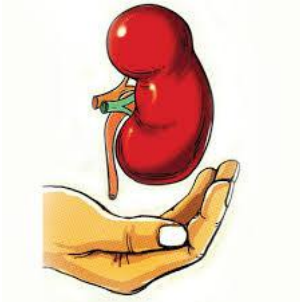
# In patients with mild to moderate COVID-19 symptoms, BUT with high risk for organ rejection:



- High-risk patient for organ rejection contains: the first 2 months of organ transplantation, Re-transplantation, Immunologically high-risk transplant patients.

- In consultation with the transplant team, the patient's immunosuppression regimen should be continued as usual.

## In patients with severe to critical COVID-19 symptoms:

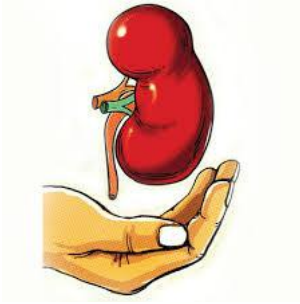


- Anti-metabolites (mycophenolate, azathioprine) and mTOR inhibitors (Everolimus, sirolimus) should be discontinued, if they are present in the patient's immunosuppressive regimen.

- In these cases, the patient's oral prednisolone should be replaced with hydrocortisone or other injectable corticosteroids at a stress dose.

- Patient calcineurin-inhibitors (CNI) (tacrolimus or cyclosporine) should be continued with the minimum blood concentration require, depending on the duration of the transplant and the type of organ transplant.

# Rational for mTor inhibitors discontinuation in severe to critical patients with COVID-19:

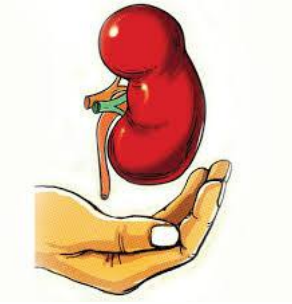


Although mTOR inhibitors have been shown to have antiviral effects on some viruses, such as cytomegalovirus (CMV) and BK (poliovirus), no effect has been seen on viruses in the corona family.

In addition, patients with Acute Respiratory Syndrome are at risk for bacterial infection, and mTOR inhibitors have lung adverse effects.

Therefore, it is currently recommended that patients with severe to critical COVID-19 infection who require a reduction in the severity of the immunosuppression regimen, be prescribed the CNI immunosuppressant regimen instead of the mTOR inhibitor if possible.

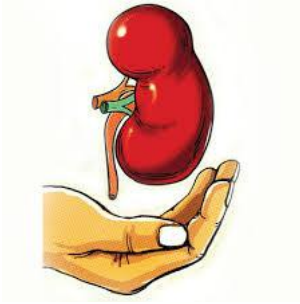
# Immuno-suppressive recommended level in recipients with moderate to critical COVID infection:



The blood levels of drugs (contain Sirolimus, Everolimus, Tacrolimus, Cyclosporine) should be monitored regularly.

**If more than two months have passed since the transplant**, the blood trough level (sampling 30 minutes before the morning dose) 4-6 ng/ml is sufficient for Tacrolimus, and 75-150 ng/ml for cyclosporine.

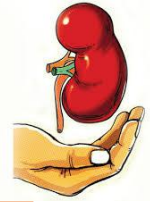
**In the first two months of high-risk immunological transplantations**, usually at the time of infection, trough blood levels of 5-7 ng/ml for tacrolimus and 150-200 ng/ml for cyclosporine are considered.
Lower trough blood levels are usually sufficient for liver recipients.



# Drug-Drug interactions

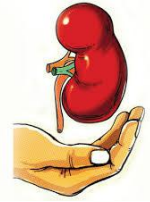
Drug-drug interactions between different drugs may occur:

- Pharmacokinetically interaction: usually affects drug metabolism; or:
- Pharmacodynamic interactions: mainly similar and cumulative side effects and sometimes antagonistic interactions.



| Interfering drug | Affecting drug | mechanism | consequence |
|---|---|---|---|
| Lopinavir/R<br>Atazanavir/R | CNIs, mTOR inhibitors | Reducing/inhibiting drug metabolism | ↑ drug level |

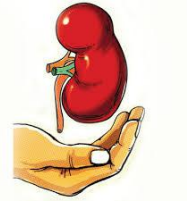
- This interaction usually begins one to two days after the start of lopinavir/r or Atazanavir/r and peaks within a few days.
- The recommended drug level monitoring is: every other day for cyclosporine/Tacrolimus/Everolimus and 7 days for Sirolimus (due to the long half-life of sirolimus).
- It is recommended to reduce the dose of these immunosuppressants based on their trough level.
- Note that based on short course of treatment with lopinavir/r or atazanavir/r, increase the dose of these immunosuppressants again after stopping the drug.



| Interfering drug | Affecting drug | mechanism | consequence |
|---|---|---|---|
| Lopinavir/R<br>Atazanavir/R | **Tacrolimus** | Reducing/inhibiting drug metabolism | ↑ drug level |

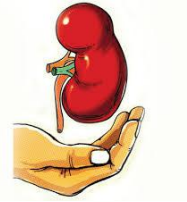
- The drug interactions are so strong that even with a single dose of 1 mg of tacrolimus once a week, most patients reach blood levels of 4-6 ng / ml.
- If the patient has a blood level of tacrolimus in this range or higher at the start of antiviral therapy, tacrolimus can be hold in the first week of treatment with lopinavir/R or atazanavir/R.
- If the patient has a Tacrolimus trough level below 3 ng/ml at the time of hospitalization, the patient should take another dose of its usual dose or a dose of 1 mg (each less), and then tacrolimus should be hold in the first week of antiviral therapy.

# Tacrolimus + Lopinavir/r or Atazanavir/r interaction



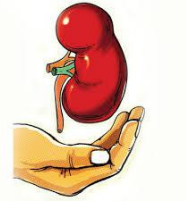
Pharmaco-kinetical interactions

- If treatment with lopinavir/R or atazanavir/R continues for more than one week, a single dose of 1 mg Tacrolimus should be given at the beginning of the second week of treatment.
- After discontinuation of these antiviral drugs, it is recommended to adjust the dose of Tacrolimus based on its blood level.
- If monitoring of Tacrolimus trough levels is not available, start Tacrolimus immediately after stopping the lopinavir/R or atazanavir/R, with the patient's basic dose.



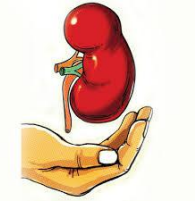
| Interfering drug | Affecting drug | mechanism | consequence |
|---|---|---|---|
| Lopinavir/R<br>Atazanavir/R | **Cyclosporine** | Reducing/inhibiting drug metabolism | ↑ drug level |

- This Drug-Drug interactions is moderate.
- A dose reduction of 5-20% is required at cyclosporine (Csp) dose.
- Among other COVID-19 antiretroviral drugs, hydroxychloroquine may increase blood levels of cyclosporine, due to the presence of two drugs that inhibit cyclosporine metabolism in the antiviral regimen, if the patient's Csp level is target range or higher, a dose reduction of about 20% or more is recommended in the daily dose of Csp.
- Start Csp immediately after stopping the lopinavir/R or atazanavir/R, with the patient's basic dose.



| Interfering drug | Affecting drug | mechanism | consequence |
|---|---|---|---|
| Lopinavir/R<br>Atazanavir/R | **Everolimus** | Reducing/inhibiting drug metabolism | ↑ drug level |

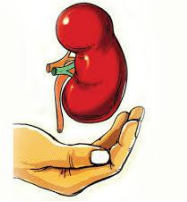
- Concomitant use of these drugs has been contraindicated in most databases.
- On the other hand, in patients with severe infection, it is recommended to discontinue Everolimus, until the infection is controlled.
- At the discretion of the transplant team, in the severe phase of infection, it is best to use CNI as an immunosuppressant instead of an mTOR inhibitor if there is a concern about transplant rejection.



| Interfering drug | Affecting drug | mechanism | consequence |
|---|---|---|---|
| Lopinavir/R<br>Atazanavir/R | **Sirolimus** | Reducing/inhibiting drug metabolism | ↑ drug level |

- Drug interactions have been relatively strong.
- A dose reduction of 90-50% is required in the dose of Sirolimus.
- On the other hand, in patients with severe infection, it is recommended to discontinue Sirolimus, and replace with CNI (Tacrolimuns,Csp) until the infection is controlled.
- Leukopenia and thrombocytopenia are common complications of Sirolimus, with COVID-19, which exacerbates the patient's condition.

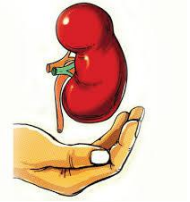
# Sirolimus + Lopinavir/r or Atazanavir/r interaction



- If the decision is to continue Sirolimus during the COVID-19 infection, if its trough level has been in the range of 4-6 ng/ml before starting antivirals, continue Sirolimus with the previous dose but with increasing dose interval to once weekly.

- Sirolimus tablets are 1 mg and cannot be crushed or dispensed. Therefore, if doses below 1 mg per day are needed, due to its long half-life, the intervals between doses should be increased.

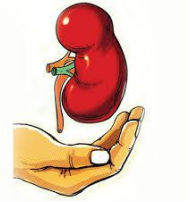
- If its trough level is higher than 6 ng / ml, Sirolimus should be discontinued during antiviral therapy, even if the course of treatment is two weeks.



# Drug interactions that increase similar side effects

## *Cotrimoxazole*

- Concurrent administration of these drugs has been linked to hematologic side effects.
- If more than six months have passed since the transplant, the corticosteroid drug can be discontinued during the coronavirus infection phase and treated.
- If less than six months have passed since the organ transplant, it is best to continue with the dose adjusted based on renal function and monitor the patient's blood count.
- In case of leukopenia (<2000/mm3), neutropenia (<1000/mm3), or thrombocytopenia (<50,000/mm3) cotrimoxazole should be discontinued.



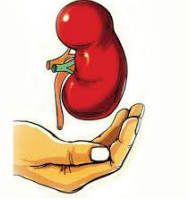
# Drug interactions that increase similar side effects

## *(Val) Gancyclocir*

- Concurrent administration of these drugs has been linked to hematologic side effects.
- If more than three months have passed since the transplant and there is no clinical suspicion of CMV infection, in a patient with hematologic complications, (val)Gancyclovir, which is prescribed for CMV prophylaxis after transplantation, can be discontinued.
- If CMV prophylaxis is necessary, it can be continued pre-emptive during the ganciclovir discontinuation period (ie the CMV PCR can be checked on a weekly basis).
- If the patient has had a heart or kidney transplant and has received a thymoglobulin injection at the time of transplantation, and less than three months have passed since the transplant, prophylaxis with (Val)Gancyclovir should be continued and blood count should be monitored.



# Drug interactions that have Antagonistic effects



Some herbal supplements, such as **echinacea**, which patients take to boost their immune system during epidemic infections, increase the risk of transplant rejection and should be avoided.