

# Prescribing practices of lopinavir/ritonavir, hydroxychloroquine and azithromycin during the COVID-19 epidemic crisis and pharmaceutical interventions in a French teaching hospital

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## ABSTRACT

**Objective** The aims of this study were to describe prescribing practices of lopinavir/ritonavir, hydroxychloroquine and azithromycin during the COVID-19 epidemic crisis (primary endpoint), then to characterise pharmaceutical interventions (PIs) targeted to these medications and evaluate the impact of these PIs on prescribers' practices (secondary end-points).

**Methods** This retrospective observational study was carried out at the University Hospital of Strasbourg (France) from March to April 2020. The analysed population excluded patients from intensive care units but included all other adult patients with COVID-19 who received at least one dose of lopinavir/ritonavir combination, hydroxychloroquine or azithromycin, while inpatients. Analyses were performed by using data extracted from electronic medical records.

**Result** During the study period, 278 patients were included. A rapid decrease in lopinavir/ritonavir prescriptions was observed. This was accompanied by an increase in hydroxychloroquine and azithromycin prescriptions until the end of March, followed by a decrease leading to the disappearance of these two medications in April. The pharmaceutical analysis of the prescriptions resulted in 59 PIs of which 21 were associated with lopinavir/ritonavir, 32 with hydroxychloroquine and 6 with azithromycin. Regarding the medication-related problems, the most frequent ones were incorrect treatment durations (n=32 (54.2%)), drug interactions with potential torsadogenic reactions (n=14 (23.7%)) and incorrect dosing (n=6 (10.2%)). From the 59 PIs, 48 (81.4%) were accepted and physicians adjusted the medication regimens in a timely manner.

**Conclusion** This study demonstrated the value—even more meaningful in a crisis situation—of a strong synergy between physicians and pharmacists for patient-safety focused practices.

## INTRODUCTION

The health crisis linked to the epidemic of Coronavirus Disease 2019 (COVID-19) caused by the new coronavirus (SARS-CoV-2) strongly mobilised healthcare institutions. This led hospitals to strengthen their organisation with the main objectives of admitting COVID-19 patients without restriction and providing optimal and safe care.<sup>1</sup>

The University Hospital of Strasbourg (UHS) was one of the first in France to be affected by SARS-CoV-2 and responded quickly to the extremely rapid kinetics of patients' admission.<sup>2</sup> Pharmacists implemented various strategies to provide pharmaceutical care, including close monitoring of medication for all the hospitalised COVID-19 patients.

No specific medication was confirmed to treat COVID-19 during the epidemic crisis.<sup>3,4</sup> The safety and efficacy of medications proposed by clinicians as part of research protocols or routine care were uncertain, and some such as lopinavir/ritonavir combination, hydroxychloroquine and azithromycin could cause serious adverse reactions.<sup>5–7</sup> Therefore, it was important for hospital pharmacists to be actively involved in evidence-based decision making regarding such medications and to assist clinicians in formulating and adjusting medication regimens in a timely manner.

The objectives of this study were first to describe prescribing practices of lopinavir/ritonavir combination, hydroxychloroquine and azithromycin during the epidemic crisis, second to characterise the pharmaceutical interventions (PIs) targeted to these medications, and third to evaluate the impact of PIs on prescribers' practices.

## METHOD

### Study design

This was a single-centre retrospective observational study conducted at UHS between 17 March and 19 April 2020. UHS is a public teaching hospital and the largest hospital in the eastern part of France, with a total of 2600 beds. The clinical department heads gave their consent to access the patients' medical records. Moreover, the hospital booklet states that “in order to enhance the management and the safety of the patients, the hospital can use data from medical records on the condition that the access remains confidential and anonymous”. Information strictly required for the purpose of the study was thus collected in an anonymised manner.

### Inclusion and exclusion criteria

The included patients were hospitalised patients in conventional units with COVID-19 (positive SARS-CoV-2 reverse-transcription PCR or chest CT

with typical imaging of COVID-19) and who received at least one dose of lopinavir/ritonavir combination, hydroxychloroquine or azithromycin.

The population analysed excluded patients from intensive care units.

### Data collection

PIs were routinely recorded in DxCare patients' electronic medical records. For the purpose of the study, data (ie, demographic data, medications, comorbidities and PIs) were extracted from DxCare using BO application (Business Object – SAP France). The outcome of each PI was retrospectively searched in patient records and classified as “implemented”, “not implemented” or “unknown”.

### Pharmaceutical intervention

Pharmaceutical analyses were structured and carried out according to a systematic and standard method including: search for potential medication redundancies, availability of medications, pathophysiological contraindications, dosages, durations, modalities and rhythms of administration, and drug interactions. The online tools used by pharmacists were: Summary of product characteristics (<http://agence-prd.ansm.sante.fr/php/ecodex/index.php>), the French national thesaurus of interactions ([https://ansm.sante.fr/Dossiers/Interactions-medicamenteuses/Interactions-medicamenteuses/\(offset\)/0](https://ansm.sante.fr/Dossiers/Interactions-medicamenteuses/Interactions-medicamenteuses/(offset)/0)), the COVID-19 drug interactions website from the University of Liverpool (<https://www.covid19-druginteractions.org/checker>), crediblemeds (<https://www.crediblemeds.org/>) and that of the reference centre on teratogenic agents (CRAT, <https://www.lecrat.fr/>).

Lopinavir/ritonavir combination, hydroxychloroquine and azithromycin were prescribed off label. To assist clinicians in better understanding and prescribing these medications, an expert group of clinical pharmacists, infectiologists, virologists and hygienists reviewed the existing literature and French consensus (on a regular basis during the study period). This group created a rational use guideline, updated several times, including duration of treatments, contraindications, monitoring, interactions and adjustment for special populations, such as pregnant women populations (for details, please see online supplemental material). Based on this guideline which followed the evolution of the French national recommendations, pharmacists and pharmacy residents formulated PIs (ie, recommendations in response to medication-related problems (MRPs)) after fully balancing clinical benefits and risks. The MRPs were encoded according to the classification of the French Society of Clinical Pharmacy.<sup>8</sup> The impact of PIs on prescribing was measured by their acceptance. Acceptance of a PI corresponded to the implementation of the pharmaceutical recommendations by the clinicians. The COVID-19 prescriptions were daily analysed and validated.

A total of seven pharmacists and eight pharmacy residents participated in the analysis of weekday prescriptions for patients with COVID-19. At night and on weekends, pharmacy residents were on site to respond to urgent needs. In case of disagreement between pharmacists and physicians, details of the clinical situations were forwarded to the expert group to resolve discrepancies.

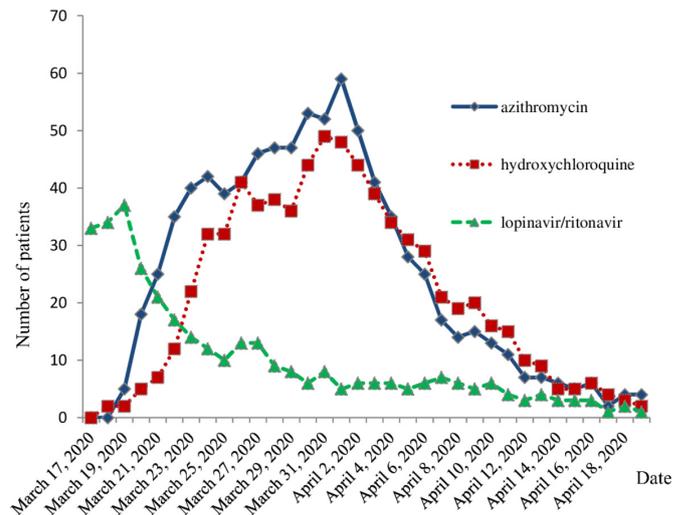
### Data analysis

Patient characteristics and study results were expressed using proportions, means with SD.

## RESULTS

### Lopinavir/ritonavir combination, hydroxychloroquine and azithromycin prescriptions

During the study period, 1449 COVID-19 patients were hospitalised, 1193 of whom were admitted to standard care units. Of



**Figure 1** Number of patients with COVID-19 treated by lopinavir/ritonavir combination, hydroxychloroquine and azithromycin from 17 March to 19 April 2020 at the University Hospital of Strasbourg, France.

these 1193 patients, 278 were treated with at least one of the three medications: lopinavir/ritonavir combination, hydroxychloroquine and azithromycin. The mean (SD) age of the patients was  $59.9 \pm 14.8$  years and the male-to-female ratio was 1.5.

Six hundred and eighty-six prescriptions corresponding to the 278 patients were completed. Pharmacists analysed and validated 483 of them (70.4%). Two hundred and three prescriptions did not benefit from pharmaceutical analysis and validation. Of these, 180 were of very short duration (prescription duration <1 day): 3, 68 and 109 for lopinavir/ritonavir combination, hydroxychloroquine and azithromycin, respectively. For the remaining 23 prescriptions, 15 patients went home and eight were transferred to intensive care units.

Figure 1 illustrates the kinetic of the prescribing practices of lopinavir/ritonavir combination, hydroxychloroquine and azithromycin at the UHS during the study period.

### Pharmaceutical interventions

Fifty-nine PIs (12.2% of the analysed prescriptions) were performed for 53 patients (19.1%). The mean age of these patients was  $58.0 \pm 14.6$  years and the male-to-female ratio was 1.9. The numbers of patients, prescriptions and PIs are presented in table 1.

Regarding the MRPs, the most frequent ones were incorrect treatment durations ( $n=32$  (54.2%)), torsadogenic drug interactions ( $n=14$  (23.7%)) and incorrect dosing ( $n=6$  (10.2%)), respectively. With regard to the 14 torsadogenic drug interactions, the following measures were taken: implementation of electrocardiographic (ECG) monitoring in seven cases, discontinuation of medication in six cases and change of medication in one case. No non-torsadogenic drug interaction was detected during the study period.

From the 59 PIs, 48 (81.4%) were accepted. In five cases (8.5%), the outcome of the proposed interventions was unknown, while in six cases the PIs were not implemented (four PIs were rejected by the physicians and in two cases the patients were transferred). The details of MRPs and PIs are presented in table 2. In addition, table 3 provides concrete examples.

**Table 1** Numbers of COVID-19 patients, prescriptions and pharmaceutical interventions, University Hospital of Strasbourg, France

	All targeted medications	Lopinavir/ ritonavir	Hydroxychloroquine	Azithromycin
Number of patients	278*	76	140†	152†
Baseline patients characteristics	Mean (SD) age: 59.9±14.8 years Female n=112 (40.3%), male n=166 (59.7 %); sex ratio 1.5			
Number of prescriptions analysed/total number of prescriptions	483/686	79/86	214/290	190/310
Number of patients with PIs*	53	21	26	6
Baseline characteristics of the patients with PIs	Mean (SD) age: 58.0±14.6 years Female n=18 (34.0%), male n=35 (66.0 %); sex ratio 1.9			

\*From 1193 patients hospitalised in standard care units.

†77 patients treated with hydroxychloroquine/azithromycin combination.

PIs, pharmaceutical interventions.

## DISCUSSION

The therapeutic management of COVID-19 patients was a major challenge during the COVID-19 epidemic crisis due to the lack of medication fully tested for safety and efficacy.<sup>9</sup> In order to best assist clinicians, rational use guidelines were developed by a multidisciplinary group of experts, including pharmacists who played a key role in drafting them. Based on these guidelines, pharmacists analysed prescriptions and contributed in optimising medication prescriptions of COVID-19 patients which were complex in terms of dosage, duration of treatment, drug interactions and management of adverse effects. During the study period, 278 patients were included. A rapid decrease in lopinavir/ritonavir prescriptions was observed. In the meantime, the prescriptions of hydroxychloroquine and azithromycin increased until the end of March, followed by a decrease leading finally to the disappearance of these two medications in April. The analysis of the prescriptions resulted in 59 PIs of which 21 were associated with lopinavir/ritonavir combination, 32 with hydroxychloroquine and six with azithromycin.

For lopinavir/ritonavir combination, a randomised controlled trial in about 200 patients published on 18 March 2020 showed that lopinavir/ritonavir combination compared with standard care did not demonstrate any benefits in terms of resolution of clinical symptoms or difference in mortality at 28 days.<sup>10</sup> Following this publication, lopinavir/ritonavir treatment decreased in our centre as shown in figure 1.

The use of hydroxychloroquine exposes patients to numerous adverse reactions such as fulminant hepatic insufficiency, severe skin reactions and ventricular arrhythmia.<sup>6 11 12</sup> These effects increase with prolonged use at high dosage. Special care is therefore essential in patients, in particular for those with congenital or acquired QT prolongation and/or with risk factors (heart disease, bradycardia, hypokalaemia, hypomagnesaemia, etc).<sup>13</sup> Concerning azithromycin, it is also essential to avoid other medications at risk of QT prolongation, risk which is also increased in cases of hypokalaemia, hypomagnesaemia or bradycardia.<sup>14</sup> The widespread publicity of small uncontrolled studies, which suggested that the combination of hydroxychloroquine with azithromycin was successful in clearing viral replication, led to a significant proportion of patients (n=77 patients) with the two medications in our hospital.<sup>15 16</sup> Obviously, it exposed them to an enhanced risk of QT prolongation and adverse events.<sup>6 7</sup>

From the beginning of April, there was a significant reduction in the number of prescriptions of hydroxychloroquine and azithromycin. This cautious attitude towards the two medications anticipated the latest publications which showed not only an absence of therapeutic benefit but also a potential harm with the use of hydroxychloroquine (with or without azithromycin) in hospitalised patients with COVID-19. In

this regard, a multinational analysis registry, including 96 032 patients published in the *Lancet*, showed a decrease in inpatient COVID-19 survival and an increase in ventricular arrhythmias. However, the methodology of this publication appeared controversial and the *Lancet* issued an “Expression of concern” to alert readers and finally withdrew the publication.<sup>17</sup> However, other studies in the meantime concluded that hydroxychloroquine had no beneficial effects in patients with COVID-19.<sup>18</sup> The National Health Service (NHS) in the UK, for example, decided to stop enrolling participants to the hydroxychloroquine arm of the RECOVERY (Randomised Evaluation of COVID-19 thERapY) trial after releasing preliminary results concerning a total of 1542 hospitalised patients.<sup>19</sup>

The most common MRPs in this study were duration of treatment, drug interactions and inappropriate dosing. These data differ from the literature, which usually primarily reports sub-optimal dosing, inappropriate administration modalities and non-compliance with guidelines.<sup>8 20 21</sup> The main reason for these differences was the changing scientific attitude regarding therapeutic strategies, dosage and duration of treatment during the epidemic crisis. It should be noted that PIs related to torsadogenic drug interactions were remarkably represented (23.7%). Although the level of severity of the MRPs was not analysed in this study, it is certain that such medication interactions represented the highest clinical risk. The very high rate of physician acceptance of PIs (85.7% of cases) is indicative of this clinical risk.

The overall average acceptance rate of clinical pharmacists' interventions was 81.4%. Regarding studies with a setting of clinical pharmacists, this rate of acceptance is in agreement with the literature.<sup>7 19 20</sup> The main reason for this level of acceptance reflects in our opinion the accepted integration of clinical pharmacists into the medication management of patients. In addition to PIs, clinical pharmacists provided continuing education and advice for both clinicians and nurses during the epidemic crisis. Furthermore, they also gave continuous information about updated guidelines and medication supply availability.

Our study has strengths and limitations.

Regarding the strengths, some COVID-19 studies described that clinical pharmacists analysed prescriptions and provided feedback to physicians about medication use-related problems,<sup>1 22</sup> but none specifically investigated the impact of pharmaceutical analysis on prescribing practices for lopinavir/ritonavir, hydroxychloroquine and azithromycin. The PIs, performed during this period, were potentially safe for the patients. Pharmacists were thus able to demonstrate their expert role, especially in the management of drug interactions.

Concerning the limitations, we did not include patients treated in intensive care units (n=316 patients treated at least with

**Table 2** Pharmaceutical interventions performed in COVID-19 patients treated with lopinavir/ritonavir combination, hydroxychloroquine or azithromycin and characterisation of the associated medication-related problems, University Hospital of Strasbourg, France

	Lopinavir/ritonavir			Hydroxychloroquine			Azithromycin					
	PIs* implemented	PIs* not implemented	Outcome unknown	Total	PIs* implemented	PIs* not implemented	Outcome unknown	Total	PIs* implemented	PIs* not implemented	Outcome unknown	Total
Medication-related problems												
Non-conforming treatment duration	17		2	19	6	1	1	8	4	1		5
Incorrect dosage	1			1	1	3		4		1		1
Drug interaction with:	1			1	11		2	13†				
Azithromycin	1			1	1		2	3				
Erythromycin					2			2				
Rovamycin					1			1				
Haloperidol					1			1				
Tiapride					1			1				
Cyamemazine					1			1				
Hydroxyzine					4			4				
Non-optimal drug intake plan					1			1				
Hydro-electrolytic disorders					5			5				
Error related to computerisation					1			1				
Total number of PIs	21				22			23	9			66.7%
Outcome of interventions (% of acceptance)	90.5%				78.1%				66.7%			

\* PIs, pharmaceutical interventions.

†No ECG carried out to assess the QT interval before the PIs were performed. ECG, electrocardiogram.

**Table 3** Examples of medication-related problems and pharmaceutical interventions, University Hospital of Strasbourg, France

Medication	Examples of pharmaceutical interventions
Lopinavir/ritonavir combination	Lopinavir/ritonavir 400 mg/100 mg combination was prescribed twice a day in association with azithromycin 500 mg on day 1 (D1) then azithromycin 250 mg D2 to D5. Both medications have the potential for QT prolongation and/or torsade de pointe (possible risk for lopinavir; known for azithromycin). Clinical monitoring by electrocardiogram was recommended and accepted by the physician.
Hydroxychloroquine	Hydroxychloroquine 200 mg twice a day was prescribed to a patient on hydroxyzine 50 mg every evening for sleep disorders. This association is contraindicated due to an increased risk of ventricular rhythm disorders, in particular torsade de pointe. The substitution of hydroxyzine with oxazepam 10 mg every evening was recommended and accepted by the physician.
Azithromycin	Azithromycin 500 mg every morning was prescribed for 6 days. According to the marketing authorisation, the recommended dosage was azithromycin 500 mg D1 then azithromycin 250 mg D2 to D5. The overdose was reported to the physician but the prescription was not modified.

one of the three medications: lopinavir/ritonavir combination, hydroxychloroquine or azithromycin). Queries for automated retrieval of data from the intensive care medical records were not possible. However, we checked that these patients benefited from an analysis of their prescriptions during their hospital stay, a necessary condition to identify potential adverse drug reactions, to adjust regimens in a timely manner and ultimately to ensure the safe use of medications. Second, despite daily analysis, 203 prescriptions extracted from Dxcare did not benefit from pharmaceutical analysis and validation. Several explanations can be given. First, when using hydroxychloroquine or azithromycin, physicians generated two prescriptions, one corresponding to the loading dose on the first day and the other to the maintenance dose. We admit that some loading dose prescriptions were not immediately intercepted by pharmacists. Second, some patients fortunately went back home. Finally, due to a deterioration in their clinical condition, other COVID-19 patients were transferred to intensive care units. However, the daily involvement of pharmacists in the follow-up of these patients in intensive care units was, as previously mentioned, just as important as in other COVID-19 wards.

## CONCLUSION

As the COVID-19 epidemic crisis became more severe, the management of patients' medications led practitioners to use off-label therapies in their daily practice. To avoid MRPs, daily pharmaceutical validation of COVID-19 medications was decided *pon*. Although clinical pharmacists did not follow up the impact of their PIs on the evolution of the clinical condition of the patients, many of the interventions highlighted significant drug interactions, including those related to the combination of hydroxychloroquine with torsadogenic medications.

## Key messages

### What is already known on this subject

- ▶ No specific medication was confirmed to treat COVID-19 during the epidemic crisis.
- ▶ The safety and efficacy of medications proposed by clinicians as part of research protocols or routine care were uncertain.

### What this study adds

- ▶ Pharmaceutical interventions highlighted significant drug interactions, including those related to the combination of hydroxychloroquine with torsadogenic medications.
- ▶ These interventions illustrate the value—even more meaningful in a crisis situation—of a strong synergy between physicians and pharmacists for patient-safety focused practices.

Recently, because of an unfavourable risk/benefit ratio regarding COVID-19 patients, the French authorities no longer allow hydroxychloroquine to be prescribed and dispensed outside the framework of marketing authorisations.<sup>23</sup> This latest update demonstrates that our strategy of strengthening the monitoring of COVID-19 medications with high potential clinical impact was adapted to this unique crisis situation.

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## Guidelines March

## COVID-19

**To date, current data do not allow highlighting a treatment to standard therapeutic management.  
Clinical trials are underway**

**This document incorporates the latest French national recommendations.  
Assessing the risks/benefits of each prescription remains fundamental.**

- Confirmed non-serious or ambulatory COVID+ patients : **standard therapeutic management**
- Confirmed COVID+ patients hospitalized with signs of severity (requiring supplementary oxygen therapy) :  
except patient in critical condition not subject to resuscitation
  - ✓ **STANDARD THERAPEUTIC MANAGEMENT**
  - ✓ **HYDROXYCHLOROQUINE 200mg, 2 tablets twice daily at D1 then one tablet twice daily from D2 to D5** in the absence of contra-indications (risk of ventricular rhythm disorder) and after completing an ECG to evaluate the QT interval. (Yao X. et al. *Clinical Infectious Diseases*; doi.org/10.1093/cid/ciaa237)
  - ✓ **HYDROXYCHLOROQUINE + AZITHROMYCIN**
    - **Please note: the association increases the risk of cardiac toxicity.**
    - The absence of data on this association justifies that its use can enter into a therapeutic evaluation process
  - ✓ **LOPINAVIR/RITONAVIR 200mg/50mg 2 tablets twice daily during 5 days**, in the absence of contra-indications.
    - **Only in patients with symptoms for last than 10 days** (Cao B. et al. *NEJM*, DOI: 10.1056/NEJMoa2001282)
    - **Avoid lopinavir/ritonavir and hydroxychloroquine association due to an increased risk of cardiac toxicity.**
      - **Contact the clinical pharmacist of your care units to set up these treatments.**
- Confirmed COVID+ patients hospitalized in intensive care units with respiratory distress syndrom :
- ✓ **IDEM ABOVE**
- ✓ **REMDESIVIR IV 200mg loading dose then 100mg / d for 10 days**  
The request for access to treatment must be made directly by the department doctor to the pharmaceutical laboratory via the following link :<https://rdvcu.gilead.com/>  
You will also find on this link, the restrictions on this drug availability.

**For the delivery to the pharmacy part, it is imperative to faithfully enter the informations below during the request so that the treatments can be delivered.**

If Approved - Where are we shipping the investigational drug?

To whom are we delivering the product (The contact below must be reachable with 24 hour availability)

Pharmacy/Hospital Name\*

HOPITAUX UNIVERSITAIRES POLE LOGISTIQUE PHARMACIE

Pharmacist/Pharmacy Contact Name\*

DR BENEDICTE GOURIEUX

Address\*

70 RUE DE L'ENGELBREIT - 67200 STRASBOURG

E-Mail\*

pharmacie-contact@chru-strasbourg.fr

Phone\*

0369553368

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- ✓ **Immunomodulatory treatments, not first-line**, under evaluation in therapeutic trials.

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## Guidelines April

## COVID-19

**To date, current data do not allow highlighting a treatment to standard therapeutic management.  
Clinical trials are underway**

**This document incorporates the latest French national recommendations.  
Assessing the risks/benefits of each prescription remains fundamental.**

- Confirmed non-serious or ambulatory COVID+ patients : **standard therapeutic management**
- Confirmed COVID+ patients hospitalized with signs of severity (requiring supplementary oxygen therapy) : except patient in critical condition not subject to resuscitation
- ✓ **STANDARD THERAPEUTIC MANAGEMENT**
- ✓ **HYDROXYCHLOROQUINE 200mg** in the absence of contra-indications (risk of ventricular rhythm disorder) and after completing an ECG to evaluate the QT interval
- ✓ Protocol for therapeutic use (PTU) – French national recommendations – date : 3/30/20
- ✓ **HYDROXYCHLOROQUINE + AZITHROMYCIN**
  - **Have not been proven effective and increase the risk of QT interval prolongation.**
  - **Must only be prescribed as part of a clinical trial.**
- ✓ **LOPINAVIR/RITONAVIR 200mg/50mg**, in the absence of contra-indications.
  - **Protocol for therapeutic use (PTU) – French national recommendations** – date : 3/30/20
  - **Only in patients with symptoms lasting more than 10 days.** (Cao B. et al. NEJM, DOI: 10.1056/NEJMoa2001282)
  - **Avoid lopinavir/ritonavir and hydroxychloroquine association due to an increased risk of cardiac toxicity.**
    - **Contact the clinical pharmacist of your care units to set up these treatments.**
- Confirmed COVID+ patients hospitalized in intensive care units with respiratory distress syndrom :
- **IDEM ABOVE**
- **REMDESIVIR IV** : limited indications
- European Discoverytrial Discovery
- Pregnant women or children under 18 years with confirmed COVID-19 and severe manifestations of the disease: <https://rdvcu.gilead.com/>

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