Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments

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ABSTRACT

Patients with COVID-19 are sometimes already being treated for one or more other chronic conditions, especially if they are elderly. Introducing a treatment against COVID-19, either on an outpatient basis or during hospitalization for more severe cases, raises the question of potential drug-drug interactions. Here, we analyzed the potential or proven risk of the co-administration of drugs used for the most common chronic diseases and those currently offered as treatment or undergoing therapeutic trials for COVID-19. Practical recommendations are offered, where possible.

Keywords: Pharmacokinetics; Pharmacodynamics; Adverse events; Therapeutic drug monitoring; Hydroxychloroquine; Lopinavir

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, at the end of 2019 [1] The patient population most affected by severe forms of COVID-19 includes not only the elderly (> 65 years), but also younger people living with co-morbidities, such as obesity, high blood pressure, and type 2 diabetes [2–4] Most of these particularly fragile patients benefit from chronic treatment, often combining several drugs. The worsening of COVID-19 sometimes requires treatment in intensive care units (ICUs), combining sedation and mechanical ventilation. In the most serious forms, multiorgan failure can be observed (e.g. cardiac, renal, and hepatic, along with thrombotic issues) [5–7], of which the management will require polypharmacy (curares, benzodiazepines, opioids, anticoagulants, calcium channel blockers, glucocorticoids, etc.). Several therapeutic strategies (more than 300 clinical trials) are currently being tested in COVID-19 for various stages of the disease [8]. Some of the drugs being tested are likely to interact with chronic treatment as well as the treatment used in the patient's resuscitation. Such drug-drug interactions largely result from their pharmacokinetic properties (e.g. induction or inhibition of cytochrome P450 (CYP) isoenzymes, competition in renal elimination), as well as their pharmacodynamic properties (e.g. QT prolongation). In addition to these interactions, there is a large inflammatory component in COVID-19 patients, which can modify the pharmacokinetic behavior of the drugs used (e.g. down-regulation of CYP isoenzymes, organ failure, modification of plasma protein concentrations) [9,10]. The objective of this review is to describe the clinically relevant drug-drug interactions between COVID-19 candidate drugs and those used in patients suffering from other diseases.

GENERAL INFORMATION ON THE RISK ASSESSMENT AND POSSIBLE STRATEGIES TO MINIMIZE DRUG-DRUG INTERACTIONS

The risk of a drug-drug interaction should be systematically assessed when initiating a treatment for COVID-19 in a patient already receiving chronic treatment. In terms of pharmacokinetic interactions, good knowledge of the drug's characteristics related to drug metabolizing enzymes or transporters (substrate, inhibitor, or inducer) makes it possible to anticipate the risk of increasing or decreasing plasma exposure. The amplitude of the interaction can be determined from (1)

dedicated interaction studies, most often conducted according to a cross-over design, (2) published retrospective studies or clinical case reports, and/or (3) *in-vitro/in-vivo* extrapolation using prediction methods [11,12]. In that latter case, a ratio of AUCs (Rauc) can be calculated, which is the estimated steady-state AUC of the drug when associated with the inhibiting or inducing drug above the estimated steady-state AUC of the drug when the drug is given alone. Theoretical variations in exposure, together with the known concentration-effect relationship and the existence of a narrow therapeutic margin, may help in anticipating the risk and its nature. However, these approaches have limitations. Interaction studies are generally carried out in healthy volunteers and the amplitude of the interaction may be different in the target population. Furthermore, most of these methods do not allow the evaluation of multiple interactions, despite frequent polypharmacy in patients with chronic diseases and comorbidities. Therapeutic drug monitoring (TDM) can help to individually adjust the dose to optimize treatment.

The risk of pharmacodynamic interaction comes from additivity or antagonism of the effects of the drugs. Knowledge of the mechanisms of action of the co-administered drugs, as well as their safety profiles, can help in anticipating the risk, such that the treatment is adapted and/or an appropriate therapeutic alternative is proposed. Post-market pharmacosurveillance provides particularly useful information from this point of view.

RELEVANT PHARMACOKINETIC AND PHARMACODYNAMIC ELEMENTS ABOUT DRUGS CURRENTLY PROPOSED FOR COVID-19 TREATMENT

The drugs currently offered for the treatment of COVID-19 are either already known, but used in a context different from that of their usual use (drug repositioning/repurposing), or drugs currently under clinical development, for which little data are yet available. Thus, their definitive positioning is still not well known, and they are sometimes used at different stages of the disease. As such, they can be co-prescribed either with the patient's chronic treatments or with treatments initiated during the acute phase of the disease as part of hospitalization, sometimes in ICUs. Thus, it is important to consider not only their pharmacokinetic and/or pharmacodynamic properties, but also the impact that patient-related factors can have on their effects. For example, patients suffering from COVID-19 sometimes present with a major inflammatory state that can modify

drug pharmacokinetics or they are not able to swallow, rendering drug absorption highly erratic (gastric tube, crushed tablets ...).

Herein, we describe the main characteristics of drugs being used or tested at the date of this review.

Hydroxychloroquine

The antiviral mechanism of hydroxychloroquine is poorly understood. It may act by inhibiting the pH-dependent entry of certain viruses into host cells or by blocking the replication of enveloped viruses by inhibiting the glycosylation of envelope proteins [13]. It also has anti-inflammatory and immunomodulatory activities by regulating the production of TNFα, interferon, and other cytokines. To date, clinical efficacy of the drug appears limited with no difference in a large post-exposure prophylaxis study and the announcement of the discontinuation of the hydroxychloroquine arm in the RECOVERY trial conducted in hospitalized patients [14]. Due to its inhibitory effect on hERG potassium channels, it can increase the QT interval [13,15]. It also has hypoglycemic effects, sometimes severe, in non-diabetic subjects.

Hydroxychloroquine accumulates in erythrocytes with a variable blood/plasma ratio (estimated to be 7.2 ± 4.2 at steady state, probably lower at the start of treatment) and has a high volume of distribution, reflecting extensive tissue distribution [16]. Its metabolism is hepatic but has not been precisely characterized, the implication of CYP3A4/5, 2D6, and 2C8 being extrapolated from chloroquine data. Its elimination half-life is estimated to be > 40 days. Thus, steady-state concentrations are theoretically reached only after several months of treatment and not after 10 days, as currently recommended for COVID-19, even though a loading dose may allow partially overcoming this difficulty. Nevertheless, the main risk of drug-drug interactions with hydroxychloroquine is pharmacodynamic in origin, associated with its effect on QT prolongation.

Viral RNA polymerase inhibitors: favipiravir and remdesivir

Favipiravir and remdesivir are two prodrugs that are active after intracellular phosphoribosylation. They act as false substrates during the viral transcription prompting chain termination and then displaying antiviral activity.

Favipiravir shows marked hepatic metabolism, mainly mediated by aldehyde oxidase, but it is not a substrate for CYPs. Its exposure may be increased in the Asian population because of a genetic polymorphism of aldehyde oxidase. Its elimination is mainly renal, mostly as metabolites (82-92%). It is a weak inhibitor of several metabolic and transport pathways but only its effect on CYP2C8 can have clinical consequences for substrates for which the exposure may be increased [17]. The risk of QT prolongation with favipiravir is considered to be low [18] but regular monitoring is necessary when it is used in combination with other QT-prolonging drugs.

Remdesivir, administered as a prodrug, is rapidly metabolized by a hydrolase to a nucleoside monophosphate derivative that enters the target cell and undergoes activation to the triphosphorylated derivative. The plasma half-life of remdesivir is short (~ 1h), whereas that of its intracellular phosphorylated metabolite is long (~ 35h) [19]. According to *in vitro* studies, remdesivir is a substrate and inducer of several CYPs and transporters [18].

In view of available data on the inducing and/or inhibiting potential of its metabolites, no pharmacokinetic interaction is expected. Similarly, as remdesivir is very rapidly metabolized, its plasma exposure is low, and few significant interactions are therefore expected *in vivo*. Only strong enzyme inducers are likely to significantly reduce its exposure and are therefore not recommended. However, the impact of a strong inducer on the concentration of the active intracellular metabolite is not known to date.

HIV protease inhibitors: Lopinavir/ritonavir (lopinavir/r)

Lopinavir is an inhibitor of the HIV-1 and 2 proteases, leading to the production of immature, non-infectious virions by inhibiting the cleavage of viral polyproteins. Ritonavir is combined with lopinavir as a pharmacokinetic "booster" due to its powerful inhibitory effect on CYP3A4. Lopinavir exhibits high pharmacokinetic variability, linked to a significant CYP-dependent first-pass effect in the liver, and has a short half-life (5 to 6 h). Lopinavir and ritonavir both have enzyme-inducing effects but are mainly substrates and inhibitors of CYP3A4 and P-glycoprotein (P-gp) and the BCRP and OATP1B1 transporters [20]. As such, they are responsible for numerous

drug-drug interactions, most often increasing the exposure and toxicity of co-administered drugs. This explains why they must be used with extreme caution in fragile and polymedicated patients [18]. Caution should be exercised when lopinavir/r is combined with drugs known to increase the PR or QT interval, as it also causes conduction and repolarization disorders by itself.

Interferon

Type I interferon (interferon beta-1b particularly) has also been proposed as a monotherapy or in combination with lopinavir/ritonavir and ribavirin for COVID-19 treatment. In an open-label phase II randomised trial, this combination has been shown to decrease the time to nasopharyngeal swab negativation (from 12 to 7 days) [21]. The potential for pharmacokinetic drug-drug interaction appears low with interferon based on their limited interactions with CYPs.

Interleukin-6 (IL-6) inhibitors: tocilizumab and sarilumab

Tocilizumab and sarilumab are monoclonal antibodies (Ab) that bind to and inhibit the soluble and membrane receptors for IL-6. They are mainly indicated for the treatment of rheumatoid arthritis, but tocilizumab is also indicated for the severe cytokine release syndrome induced by CAR-T cells. Due to their long half-life (up to 16 days for tocilizumab), steady state is not reached after one or two administrations.

Although not yet studied in the specific context of COVID-19 infection, it is known that the expression and activity of the hepatic isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4 are reduced by certain cytokines, in particular IL -6 [22,23]. Thus, one cannot rule out that anti-IL6 treatment can restore the activity of these isoenzymes and thus modulate the metabolism of their substrates.

Anakinra

Anakinra is an IL-1 alpha and beta competitive inhibitors on IL-1 type I receptors. Because IL-1 is a pivotal inflammatory cytokine found in plasma and synovial fluid, the drug is indicated in

inflammatory diseases such as rheumatic arthritis [24]. During the inflammatory phase of COVID-19, Anakinra might act as a symptomatic treatment.

The main elimination process of the drug is through kidney. As for IL-6, IL-1 might downregulate CYPs expression and anakinra may the restore the CYP-mediated metabolism of drugs previously reduced during the inflammatory process.

Azithromycin

Azithromycin is an antibiotic belonging to the macrolide family that acts by inhibiting protein synthesis by binding to the 50S ribosomal subunit [25]. This antibiotic is used in patients with COVID-19 to cover the risk of secondary bacterial infection. Azithromycin may also have immunomodulatory activity by increasing the expression of interferon β and λ during viral respiratory infections and by moderately reducing the production of TNFα [26]. Azithromycin is widely distributed in the body, with high tissue affinity and accumulation in phagocytes. It is found mainly unchanged in bile and urine and has a long half-life, between two and four days. It is a weak inhibitor of CYP3A4, for which few or no clinically significant interactions are expected. The risk of interaction in the event of co-prescription is therefore not pharmacokinetic but pharmacodynamic, in connection with its effect on QT prolongation. As such, caution should be exercised when combining azithromycin with other molecules that increase the QT interval, such as hydroxychloroquine. Results from a recent study appear to indicate that the risk of cardiac death increases when these two drugs are combined [27].

Baricitinib

Baricitinib is a Janus-kinase inhibitor (JAK) 1 and JAK2, also inhibiting Tyrosine Kinase 2 and to a lesser extent JAK3 indicated in the treatment of moderate to severe active rheumatoid arthritis [28]. Baricitinib inhibits IL-6 induced STAT3 phosphorylation resulting in a global decrease in inflammation (which translates to a decrease in CRP). Although the drug may lead to the down-regulation of many interferon-controlled genes with a role in viral infection control, it may reduce SARS-CoV-2 endocytosis as well as decrease the inflammation phase [29,30]. A limited amount

of the drug (10%) is metabolized by CYP3A4 and it is also a substrate of Oragnic Anion Transporter 3 (OAT3), Pgp, BCRP and Multidrug And Toxin Extrusion protein 2-K (MATE2-K). Baricitinib is an inhibitor of Ornythil Cation Transporter 1 (OCT1) Apart from OAT3 and OCT1, no clinically drug-drug interaction is expected with Barictinib. A slight decrease in creatinine secretion is reported with Baricitinib resulting in an apparent decrease in estimated GFR but without any loss of renal function [28].

ASSESSMENT AND MANAGEMENT OF THE RISK OF DRUG-DRUG INTERACTIONS WITH OTHER WIDELY USED DRUGS

Antipyretics and analgesics

Paracetamol

The recommended treatment against fever for COVID-19 is paracetamol. Due to the hepatic toxicity of its metabolite, caution should be exercised when it is combined with other hepatotoxic drugs, such as lopinavir. If combined with favipiravir, the daily dose of paracetamol should not exceed 3 g, due to an increase, although modest, in its exposure [18].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

The use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, whether at analgesic or antipyretic doses, is not recommended for the treatment of COVID-19 symptoms, based on a body of clinical and scientific arguments showing an increased risk of worsening bacterial infections, with serious consequences [13]. As weak OAT3 inhibitors, diclofenac and ibuprofen might slighltly increase baricitinib exposure [28].

Opioid analgesics

Opioid analgesics are most often metabolized by several routes and form, for many, active metabolites. Tramadol is metabolized by CYP3A4 and 2D6 into several metabolites, one of which, produced by CYP2D6, is much more active than the parent compound [31]. Codeine, inactive by itself, is metabolized by CYP3A4 and 2D6. Its active metabolites (mainly morphine produced by CYP2D6) are then glucurono-conjugated to active metabolites (e.g. morphine 6-glucuronide) [32]. Oxycodone is primarily metabolized by CYP3A4 to inactive metabolites [33]. Morphine is metabolized to an inactive metabolite by CYP3A4, then by glucuronidation to several metabolites, of which one, morphine-6-glucuronide, is active [32].

Thus, the consequences of inhibition or induction of a particular metabolic pathway will depend on the existence of alternative metabolic pathways that can compensate each other, as well as the nature of the metabolites affected by the interaction (Table 1). Thus, the consequences of interactions that simultaneously affect several metabolic pathways (e.g. inhibition of CYP3A4 and CYP2D6 by lopinavir/r) are difficult to predict and studies have not always been carried out. If opioids are administered in combination with lopinavir/r, careful monitoring of patients is recommended to detect any signs of overdose or ineffectiveness and to adapt the analgesic treatment if necessary. Of note, the oral solution of Kaletra® contains alcohol (42.4%) and can increase the sedative effect of opioids.

Drugs used in cardiovascular diseases

Anticoagulants and antiplatelet drugs

The thromboembolic risk in patients with COVID-19 is high and specific recommendations have been issued jointly by the GIHP (*Groupe d'Intéret en Hémostase Périopératoire*) and GFHT (*Groupe d'étude sur l'Hémostase et la Thrombose*). The use of low-molecular weight or unfractionated heparins, depending on the situation, is recommended. Antivitamin K and direct oral anticoagulants are not recommended. They must be stopped and replaced by heparin, which, either fractionated or not, is not likely to interact with the drugs used for COVID-19 treatment [34].

Platelet anti-aggregation with low dose aspirin must be continued as long as the patient's condition warrants it. Clopidogrel, a prodrug activated by CYP2C19, must not be associated with an enzyme inhibitor such as lopinavir/r, as this may reduce its effects, and an alternative drug must be used [35].

Lipid-lowering drugs

Statins are widely used in patients with dyslipidemia and/or a history of cardiovascular events. From a pharmacodynamic point of view, their toxicity can be increased by additive effects from lopinavir/r, which is responsible for dyslipidemia (in the event of high exposure, i.e. Cmin > 8 µg/mL), myalgia, and/or elevation of CPK. Given the short duration of treatment with lopinavir/r in patients with COVID-19, only increased muscle toxicity could be an issue. Biological monitoring is thus necessary, and the dose of the statin may have to be reduced in case of an increase in CPK activity. The interruption of statins during COVID-19 treatment can also be discussed. In terms of their pharmacokinetics, statins are, to varying degrees, substrates of CYP3A4, BCRP, and OATP1B1, which are inhibited by ritonavir. Simvastatin is the strongest CYP substrate, whereas pravastatin is the least prone to interactions (36). From a practical point of view, it would be better to use pravastatin in patients with COVID-19 treated with lopinavir/r.

Anti-hypertensives

Angiotensin-converting enzyme inhibitors, sartans, and diuretics are not subject to significant pharmacokinetic interactions. Plasma exposure of dihydropyridine calcium-channel blockers, which are metabolized by CYP34, can be significantly increased when co-administered with lopinavir/r, especially felodipine, with an AUC ratio (Rauc) of 7, and nifedipine (Rauc = 3.5). Amlodipine exhibits a weaker interaction (Rauc = 2.7) and could be administered every other day if a calcium-channel blocker is needed. Data for other calcium-channel blockers are insufficient to draw any conclusions concerning their potential risks.

Plasma exposure of beta-blockers, which are often metabolized to varying degrees by CYP2D6, is increased by lopinavir/r and hydroxychloroquine. The increase with hydroxychloroquine, approximately to a two-fold Rauc, is not of great concern. The increase may be more pronounced with lopinavir/r, which is a more potent inhibitor of CYP2D6. In particular, the Rauc is 3.4 for

metoprolol, with a risk of arrhythmia or even cardiac arrest [37]. This association is thus contraindicated. The risk of an interaction between a beta-blocker with bradycardizing properties and drugs that increase the QT interval should also not be overlooked.

Drugs used in heart failure

Eplerenone is extensively metabolized by CYP3A4. As such, its exposure increases by a factor of 4.6 (Rauc) when co-administered with lopinavir/r. The interaction with spironolactone is probably weak, but not documented. Replacing eplerenone with spironolactone is thus an option worth considering.

Drugs used in angina pectoris

Nitrogen derivatives are not likely to undergo pharmacokinetic interactions with lopinavir/r or hydroxychloroquine. On the contrary, ivabradine, which is extensively metabolized by the CYP3A4 pathway, presents a significant interaction when co-administered with lopinavir/r, with an Rauc of approximately 6.7. Given the risk of severe bradycardia, this association is contraindicated. A weakly metabolized beta-blocker (atenolol) or amlodipine (half-dose in the precise context of this interaction) are good alternatives, even outside the context of interaction.

Antiarrhythmic drugs (AADs)

Vaughan-Williams class I AADs (i.e. sodium-channel blockers) are often metabolized by CYP2D6. Quinidine and propafenone exposure increase by a factor of 1.6 to 1.7 (Rauc) in the presence of lopinavir/r. Despite not being impressive, this increase may nevertheless lead to cardiac disorders, as these drugs have narrow therapeutic margins. Minimally, ECG monitoring is required and a 50% dose reduction of the antiarrhythmic may be needed. In addition, TDM is required for dose adjustment.

Class III AADs (i.e. potassium-channel blockers) are contraindicated in combination with lopinavir/r. Amiodarone is metabolized by CYP3A4, CYP2C8 and CYP2C9 and its active

metabolites by CYP3A4. Their concentrations thus increase, and cases of torsades de pointes have been reported when amiodarone is combined with protease inhibitors [38]. Dronedarone has a very strong interaction with lopinavir/r (Rauc = 16.8) and this association is contraindicated. Digoxin concentrations can be doubled in the presence of ritonavir, which inhibits P-gp. TDM and dose adjustment are necessary [39].

Oral anti-diabetics

Hypoglycemia, sometimes observed during infection with SARS-Cov2, can be worsened by hydroxychloroquine, whereas lopinavir/r can cause hyperglycemia. Overall, the glycemic control of patients with diabetes mellitus must be strengthened and the treatment adapted if necessary.

Insulin and metformin are not at risk of pharmacokinetic interaction with lopinavir/r. In contrast, sulphonylureas are substrates of CYP2C9 and their exposure can be reduced by ritonavir, which induces this isoenzyme [40]. As such, gliclazide concentrations can be halved. As glimepiride is less affected, this drug may be preferred. However, the risk is low due to the short-term treatment with lopinavir/r and will not necessarily have clinical repercussions.

Gliptins are substrates of CYP3A4, and their concentrations can be increased by lopinavir/r (for example, by a factor of 2.6 for saxagliptin). In addition, sitagliptin may induce interstitial pneumonia and increase the rate of infections (11 to 14% vs 7% on placebo) [41,42]. These two side effects could also be increased by interaction with lopinavir/r. Thus, the use of this therapeutic class in Covid-19 patients should be assessed on a case-by-case basis.

Drugs used in infectious diseases

Anti-retroviral drugs (HIV)

There is no need to modify the antiretroviral treatment of HIV patients to introduce lopinavir/r. The management of COVID-19 in HIV patients should, however, take into account the risk of interactions, in particular if the antiretroviral treatment contains drugs with pharmacokinetic boosters, such as cobicistat or ritonavir. Based on *in-vitro/in-vivo* extrapolation, there is a risk of overexposure to hydroxychloroquine, and therefore QT prolongation, when combined with

ritonavir or cobicistat. Rilpivirine can also prolong the QT interval and its association with hydroxychloroquine or lopinavir/r may be risky, despite the absence of a solid study [43]. Co-administration of lopinavir/r with other classes of antiretrovirals should be closely monitored and supported by TDM, as their plasma concentrations can change. For maraviroc, dose adjustment is recommended in the summary of product characteristics (SmPC) [44]. Lopinavir/r does not significantly modify exposure to dolutegravir or raltegravir, but its combination with bictegravir is not recommended in the absence of data [45,46].

Certain non-nucleoside reverse transcriptase inhibitors, such as nevirapine, efavirenz, and etravirine, may decrease exposure of lopinavir or hydroxychloroquine by inducing CYP3A4 [47]. Concerning remdesivir, no interaction data with antiretrovirals is currently available, but its structural proximity with tenofovir (both adenosine analogs) can lead to competition for phosphorylation and tubular elimination and they should be co-administered with prudence [48]. If a risk of interaction is suspected, stopping antiretrovirals for a few days is possible if the clinical situation related to COVID-19 is critical and justifies the implementation of treatments considered to be a priority in this context. Finally, if it is impossible to continue antiretroviral treatment *per os* (e.g. in case of respiratory assistance), it is possible to switch to molecules and/or formulations allowing administration by nasogastric tubes, while maintaining good bioavailability [18].

Treatment of viral hepatitis B and C

The initiation of treatment for hepatitis B or C is not indicated in the context of an ongoing infection with SARS-CoV-2. However, patients already receiving treatment for hepatitis may require treatment for COVID-19.

Hepatitis C treatment is based on direct-acting antivirals as part of bi- (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir) or tri- (sofosbuvir/velpatasvir/voxilaprevir) therapies, or possibly sofosbuvir/glecaprevir/pibrentasvir, in case of previous failure. Pharmacodynamically, sofosbuvir has been associated with brutal bradycardia and its association with hydroxychloroquine may be risky and requires close monitoring by ECG and of kaliemia measurement [49]. Pharmacokinetically, the risk of interaction between anti-HCV antivirals and remdesivir appears to be low. On the other hand, by inhibiting OATP1B1, CYP3A4, and P-gp, lopinavir/r may increase voxilaprevir exposure (e.g. with darunavir/r, exposure to voxilaprevir is multiplied by 2.4) and the

combination of these drugs is not recommended [50]. The combination of lopinavir/r with glecaprevir/pibrentasvir is also not recommended (exposure of glecaprevir x 4.5) [51]. Voxilaprevir inhibits intestinal CYP3A4 and increases the exposure of patients co-treated with hydroxychloroquine [50]. Glecaprevir/pibrentasvir is a weak CYP3A4 inhibitor and can cause hydroxychloroquine accumulation. In these two cases, TDM of hydroxychloroquine and ECG monitoring appears to be useful [52].

There are few interactions with hepatitis B treatments. A theoretical interaction between remdesivir and tenofovir disoproxil may occur, which, like analogues of adenosine, could lead to competition for their respective antiviral effects [53]. In addition, the safety profile of these drugs includes renal adverse effects and close monitoring should be considered in the event of combination. Lopinavir/r may also increase exposure to tenofovir, thus justifying renal monitoring [20].

Anti-tuberculosis drugs

The initiation of an anti-tuberculosis treatment is not indicated for patients with COVID-19. On the other hand, the disease can occur in patients undergoing anti-tuberculosis treatment.

The first-line strategy for the treatment of tuberculosis generally contains rifampicin, a well-known potent enzyme inducer. As a result, many interactions can occur with the drugs used to treat COVID-19 (Table 1). Co-administration of rifampicin requires strict TDM of lopinavir and hydroxychloroquine [15,20]. Exposure to remdesivir is also greatly reduced by rifampicin and their co-administration is not recommended. The persistence of enzyme induction, even after rifampicin discontinuation, makes the use of several drugs for COVID-19 very difficult for patients on anti-tuberculosis quadruple therapy. The amplitude of interactions with rifabutin is lower. However, TDM of hydroxychloroquine and lopinavir still appears to be necessary if they are used with rifabutin. The inhibitory effect of lopinavir/r on rifabutin metabolism is well documented and a dosage reduction of rifabutin may be necessary [20] if lopinavir/r is introduced for the treatment of COVID-19.

Pharmacodynamically, the additive torsadogenic effects of hydroxychloroquine and QT-prolonging anti-tuberculosis drugs should be taken into account. Hence, hydroxychloroquine and

moxifloxacin, delamanid, or bedaquiline should only be co-administered in the absence of an alternative and only with strict cardiac and electrolytic monitoring. Monitoring of liver function is also recommended, as several of these drugs are potentially hepatotoxic. The combination of hydroxychloroquine and ethambutol should also be used with caution, as ocular side effects can occur with both drugs. Finally, the possible cumulative renal toxicity between remdesivir and amikacin requires close monitoring of renal function.

In terms of pharmacokinetics, the combination of anti-tuberculosis drugs that are CYP3A4 substrates (bedaquiline and delamanid) with lopinavir/r should be used with caution. The association appears to be particularly risky for bedaquiline, for which the exposure can more than double (54). TDM of these anti-tuberculosis drugs and monitoring for QT prolongation is recommended.

Anticancer drugs: Cytotoxic, targeted therapy

Patients with cancer represent a particularly fragile population, with an excess risk of infection due to the immunosuppressive action of certain anticancer drugs and co-morbidities. Thus, the management of a SARS-CoV-2 infection in a patient with cancer, whether he/she is already treated or not, will require several precautions. The question of the specific therapeutic management of cancer depends on several factors, including the stage of the disease, life expectancy, and benefit-risk balance. Anticancer treatment must be suspended for patients with COVID-19 admitted to ICUs. Highly cytotoxic chemotherapy should also be avoided in COVID-19^{+} outpatients to reduce the risk of worsening the viral infection. Thus, the probability of combining cytotoxic chemotherapy with drugs aimed at treating COVID-19 is almost zero and the question of interactions does not arise. Targeted therapies (protein kinase inhibitors or Abs), hormonotherapy, and immunotherapy are less immunosuppressive but may potentiate the infectious risk of patients with COVID-19. These drugs present various toxicities and are involved in drug-drug interactions of both pharmacokinetic or pharmacodynamic origins [55,56].

From a pharmacodynamic point of view, additive cardiotoxicity (QT interval prolongation) may occur between certain protein-kinase inhibitors and drugs used to treat COVID-19 (hydroxychloroquine, azithromycin, lopinavir). The hepatotoxicity (cytolysis, cholestasis, or pancreatitis with lopinavir, favipiravir, remdesivir, or tocilizumab) or nephrotoxicity (risk of acute

renal failure with lopinavir/r and remdesivir) of drugs used to treat COVID-19 may aggravate those of anticancer drugs.

Protein kinase inhibitors and drugs used in hormonotherapy are extensively metabolized by the liver and are often substrates of CYP3A4 (or other CYP isoforms) and UDP-glucuronyl transferases (UGTs). These drugs are also eliminated via tubular transporters, which can give rise to competition [57]. Thus, there is a risk of pharmacokinetic interaction with certain treatments of COVID-19, such as lopinavir/r, favipiravir, or even tocilizumab, which, as described above, could modulate the activity of certain CYPs by its inhibitory effect on IL-6. These interactions could either increase exposure to and the toxic effects of the anticancer agents, or decrease their plasma concentration, with a risk of therapeutic failure.

Targeted therapies are not only victims but can also be perpetrators of interactions. Indeed, several molecules inhibit (e.g. crizotinib, lapatinib, vemurafenib) and/or induce (e.g. dabrafenib, enzalutamide) CYPs (mainly CYP3A4), UGTs, or certain drug transporters and could thus modify the bioavailability and/or elimination of lopinavir/r, favipiravir, hydroxychloroquine, or remdesivir.

The degree of interaction and its clinical relevance will depend on the duration of co-administration, the doses used, and the presence of organ failure or other co-medications. Clinical and/or biological monitoring, sometimes combined with TDM, is essential to optimize treatment.

Drugs used in organ transplantation and autoimmune diseases

Co-administration with hydroxychloroquine

Calcineurin inhibitors (tacrolimus and ciclosporin), as well as m-TOR inhibitors (everolimus and sirolimus), can cause QT prolongation [58]. One must check for the occurrence of rhythm disturbances if there is co-administration with hydroxychloroquine. Increases in exposure to hydroxychloroquine with ciclosporin have been reported in the SmPC and a similar effect is expected with everolimus [15,59]. Reciprocal inhibition could also occur with ciclosporin, tacrolimus, and m-TOR inhibitors, requiring TDM of both hydroxychloroquine and the immunosuppressants.

Co-administration with lopinavir/r

Drug-drug interactions between immunosuppressants and lopinavir/r are well known from the experience of treating HIV infection in transplant patients. Due to the strong inhibition of CYP3A and OATP1B1 and 1B3 by lopinavir/r, its association with immunosuppressants requires a drastic reduction in their dose (sometimes up to 140 times with tacrolimus) to prevent the risk of nephro- and neurotoxicity [60]. A dose of 0.5 mg per week or 0.2 mg every three days may be initially proposed for tacrolimus, and 25 mg per day or every other day for ciclosporin [61]. In addition, close TDM of immunosuppressants is essential and the assessment of the area under the concentration curve (AUC) should be considered in view of the risk of modification of the pharmacokinetic profile (a flattening of the pharmacokinetic curve has been described in this case) [62]. Similar changes are expected with m-TOR inhibitors and a decrease in the dose of sirolimus to 0.2 mg per week is recommended. Subsequent adjustment of the dose based on TDM is again essential [63]. Lopinavir/r may also decrease exposure to mycophenolic acid by inhibiting its enterohepatic cycle. In the absence of an interaction study, AUC-based TDM of mycophenolic acid may help in adjusting treatment. If the initiation of corticosteroid treatment is not indicated for the patient infected with SARS-CoV-2, at least during the viremia phase of the infection, a conservative approach is recommended for patients already being treated and the maintenance of corticosteroids at low doses is recommended. Corticosteroid metabolism is decreased by lopinavir/r and clinical and laboratory monitoring is required. A slight dose adjustment can also be considered [64].

Co-administration with other drugs used in COVID-19

No significant interactions are expected between remdesivir or favipiravir and immunosuppressants. Tocilizumab or other potent anti-inflammatory drugs used during the cytokine storm phase can modulate the inhibitory effect of inflammatory cytokines on drug metabolism. TDM of immunosuppressants, in particular that of potent substrates of CYP, is thus an essential tool for the dynamic adaptation of dosage as the inflammatory syndrome progresses [65]. Baricitinib might increase immunosuppression when co-administered with immunosuppressive drugs and association should be used with caution. Serious infections and

neutropenia has been observed when anakinra is associated with methotrexate or TNF-alpha inhibitors and their association is not recommended [24].

Drugs used in neuropsychiatric diseases

In the neuropsychiatric domain, the drug most at risk of interactions is hydroxychloroquine, due to its torsadogenic potential, adding to that of many drugs used in this setting. Despite not being formerly contraindicated, co-administration of hydroxychloroquine and most of the drugs that prolong the QT interval is not recommended. The cessation of smoking, inherent to hospitalization, can also cause unexpected drug interactions. Only the drugs for which a proven risk of interaction exists will be presented below [66].

Antidepressants

Citalopram increases the QT interval in a dose-dependent manner, from 7 ms at a dose of 20 mg, to 10 ms at 40 mg [67]. Although modest, this increase may favor the occurrence of torsades de pointes. A European decision has contraindicated the use of citalopram (and its isomer escitalopram) with any other potentially torsadogenic drugs, including hydroxychloroquine. Despite the French SmPC being less restrictive, citalopram and escitalopram should not be combined with hydroxychloroquine. However, this is easily manageable in the context of COVID-19. Indeed, as the maximum recommended duration of hydroxychloroquine treatment is 10 days, the interruption of citalopram or escitalopram for such a short period should not expose the patient to the risk of recurrence of depression. Switching to another serotonin reuptake inhibitor (SSRI) is possible, as the pharmacodynamic effect immediately replaces that of the preceding SSRI, even if the pharmacokinetic equilibrium of the new antidepressant may take some time.

The use of interferon in patients treated for depression should be discussed because of the increased risk of depression or suicidal ideation.

Anxiolytics

Hydroxyzine is an antihistamine frequently used in place of benzodiazepines in psychiatry and geriatrics for its sedative and anxiolytic properties. It has been shown to be involved in torsade de pointes in at-risk patients and is considered to be torsadogenic by the European Medicine Agency [68]. Its use with hydroxychloroquine is de facto contraindicated. It does not cause withdrawal syndrome, which makes it easier to stop if treatment with hydroxychloroquine is started. Another anxiolytic may be offered, if necessary.

Antipsychotics

Most conventional neuroleptics (haloperidol, cyamemazine, pimozide, etc.) have a documented torsadogenic potential, but their association with other torsadogenic drugs is not contra-indicated [69]. They should therefore be maintained in association with hydroxychloroquine, especially since the suspension of a neuroleptic, even for 10 days, should be avoided in a psychotic patient.

A drug for which the risk to patients with COVID-19 is not related to drug interactions, but rather the context, is clozapine. This molecule, which is indicated for refractory psychoses, is difficult to handle due to a narrow therapeutic margin and hematological toxicity. It becomes even more so in the case of COVID-19, as patients treated with clozapine are often smokers and clozapine is metabolized by CYP1A2. As the polycyclic hydrocarbons present in tobacco smoke induce CYP1A2, the dose of clozapine at equilibrium is often higher than that in a non-smoker [70,71]. When patients suddenly stop being exposed to tobacco smoke, enzyme induction is reduced, and activity returns to a basal level after two weeks. There is a risk of an overdose of clozapine if the antipsychotic treatment has been continued at the same dose. Hematological monitoring should be strengthened for these patients. TDM should allow the dose of clozapine to be adjusted.

Drugs used in addictions

Methadone shows dose-dependent cardiotoxicity, such as torsade de pointes [72]. It is therefore not recommended with hydroxychloroquine. As before, smoking cessation in hospitalized patients may lead to methadone overdose, increasing the cardiac risk.

Finally, although not a drug, it must be remembered that cocaine is an authentic torsadogenic substance, for which the combination with hydroxychloroquine could trigger rhythm disorders [73,74]. It would be useful to ask the patient whether he/she has recently used it.

Anti-migraine drugs

Although ergot derivatives (ergotamine and dihydroergotamine) are less widely used than before, they are still an option when triptans, NSAIDs, or beta-blockers are not suitable. Macrolide antibiotics can inhibit their metabolism and increase their exposure and thus their vasoconstrictor effect, with the risk of necrosis of the extremities (ergotism). As for all other macrolides, the use of azithromycin is contraindicated in case of treatment with ergot derivatives [75]. The risk is lower with ergot derivatives used in Parkinson's disease but the association should be avoided.

Anti-epileptic drugs

In this disease, the risk of interactions arises from the enzyme-inducing effect of certain old anticonvulsants, such as carbamazepine, phenytoin, phenobarbital, and related drugs (esli- and oxcarbazepine, fosphenytoin, primidone). There is very little literature on the consequences of enzyme induction on hydroxychloroquine metabolism. A case of relapse after introduction of rifampicin has been reported in a patient with lupus, and was resolved by doubling the dose of hydroxychloroquine [76]. This case remains isolated and no definitive conclusion can be drawn. Concerning the other drugs currently offered for COVID-19, the concentration of lopinavir/r may be reduced by enzyme inducers [20]. However, in the absence of a target therapeutic concentration identified in this context, dosage recommendations cannot be made. As a general rule, anticonvulsant therapy must not be discontinued, and this equally applies to patients with COVID-19.

Thyroid hormones

An isolated case report has described the disequilibrium of thyroid treatment in association with the fixed combination of chloroquine/proguanil [77]. The mechanism of the interaction was not

identified but a metabolic interaction seems unlikely. To date, no interaction between hydroxychloroquine and thyroid hormones has been reported.

Cases of thyroid imbalance have been described with protease inhibitors, attributed to the inducing effect of ritonavir [20]. As the inertia of hormonal balance is at least two weeks and the inducing effect takes two weeks to manifest, treatment with lopinavir/r is not expected to have a significant impact.

Respiratory diseases

Anti-asthmatics

In its recommendations on treatment during the COVID-19 epidemic, the SPLF (*Société de Pneumologie de Langue Française*) recommends that drugs for the chronic treatment of asthma and chronic obstructive pulmonary disease (COPD) must be continued at an effective dose to avoid exacerbation of the disease. Furthermore, clinical trials using inhaled medications usually prescribed for asthma or COPD are underway for severe forms of COVID-19.

The main pharmacological classes used for the treatment of exacerbations are corticosteroids, β2-mimetics, and anticholinergic bronchodilators. These drugs are most often administered by inhalation and, since systemic passage is low, this theoretically limits the risk of drug interactions if they were to be co-administered with drugs used for COVID-19. A few observations nonetheless call for caution: fluticasone undergoes considerable metabolism mediated by CYP3A4. After nasal administration, ritonavir was shown to increase its plasma exposure by more than 100 times. Concomitant administration of fluticasone and ritonavir should thus be avoided based on published cases of Cushing's syndrome with this combination [78].

Budesonide is mainly metabolized by CYP3A4 and a significant increase in its exposure can be observed with strong inhibitors of CYP3A4. The same caution as above is therefore necessary for lopinavir/r. Beclometasone undergoes very rapid pre-systemic metabolism by esterases, without the intervention of CYP P450. Systemic exposure of salmeterol may be increased by strong CYP3A4 inhibitors, even if it is only inhaled [79]. In this case, there may be an increased risk of

developing the systemic effects of salmeterol, such as prolongation of the QT interval and palpitations.

The chronic treatment of asthma also relies on corticosteroids and β2-mimetics, administered by the oral route, as well as anti-leukotrienes (montelukast) and, more rarely, theophylline. Severe asthma may require the use of various monoclonal antibodies, administered by injection. For these drugs administered by the general route (oral or injectable), the risk of interaction with the drugs used in the context of COVID-19 appear to be low. Montelukast is metabolized by CYP2C8 and, to a lesser extent, 2C9 and 3A4. Combination with strong CYP2C8 inhibitors increases its AUC by a factor of 4, but without the need to adjust the dose, and itraconazole, a strong inhibitor of CYP 3A4, leads to a non-significant increase in systemic exposure of montelukast [80]. Thus, even if its combination with lopinavir/r can theoretically increase its exposure, the risks of side effects are limited. Bambuterol is hydrolyzed to terbutaline by a non-CYP-dependent mechanism and terbutaline is poorly metabolized. These two medications are thus not at risk for metabolic interactions. Theophylline is a drug with a narrow therapeutic margin, of which the metabolism mainly depends on CYP1A2, CYP2E1, and CYP3A4. Lopinavir/r may therefore change its exposure and should be used with caution. Monoclonal antibodies, eliminated by non-CYP-dependent pathways, do not expose patients to a risk of interaction.

Antitussive drugs

Although a productive cough must be respected, a non-productive cough can be managed by antitussives on an on-demand basis and for short periods, thus minimizing the risk of drug-drug interactions. Pholcodine should not be used since there is a risk of sensitization to the curares used in anesthesia.

Drug-drug interactions in the context of critical care

The strategy for the specific management of SARS-CoV2 infection for patients admitted to ICUs is currently based on the recommendations issued in early March 2020 by a group of experts [81]. However, these recommendations remain cautious and underscore that the management of patients has thus far "not been clearly determined" and that the therapies suggested are only proposed

treatments. Indeed, remdesivir, lopinavir/r, and hydroxychloroquine can be used, depending on the situation, in particular in the context of therapeutic trials currently underway for the objective evaluation of these molecules, as well as other drugs that target hyper-inflammation (corticosteroids, tocilizumab).

The management of acute respiratory distress syndrome (ARDS) does not differ much from the usual practices in this area. It is based on sedation-analgesia adapted to the ventilation needs of the patients [82]. The molecules used for sedation include propofol, midazolam, and dexmedetomidine. Analgesia is mainly based on fentanyl, sufentanil, or ketamine. Finally, curarization based on cisatracurium is implemented, when necessary. Antibiotic therapy (most often with 3rd generation cephalosporins or penicillin, sometimes combined with macrolides) and anticoagulation (most often with enoxaparin) are frequently associated.

Sedation-analgesia is adapted in real time to the patient's response. However, clinical experience indicates that patients with SARS-CoV2 may require higher doses of sedation than those with ARDS secondary to other etiologies (e.g. influenza pneumonia). Thus, the question of possible drug-drug interactions with the specific treatments of SARS-CoV2 is somewhat less important than the impact of the underlying terrain, characterized by a very marked hyper-inflammatory state (patients who are much more febrile, for longer periods, with very high levels of inflammation molecules, severe ARDS distant from the infectious phase, etc.), especially in severe forms [83].

An increase in pulmonary capillary permeability is a characteristic of ARDS, a consequence of the joint effects of inflammation and several other factors [84,85]. These effects are not limited to the lungs, however, and any inflammatory condition is accompanied by damage to the vascular endothelium, resulting in fluid leakage from the vascular compartment to the interstitial tissues. Pharmacokinetically, this phenomenon increases the volume of distribution of water-soluble drugs and therefore decreases their systemic exposure [86]. Among the sedation and analgesia drugs cited above, those with a low steady-state volume of distribution (Vdss) are cisatracurium (0.1 - 0.2 L/kg) and midazolam (0.7 - 1.2 L/kg). They are therefore particularly concerned by the risk of under-exposure linked to a hyper-inflammatory state. Propofol (1.8 - 5.3 L/kg), fentanyl (Vdss 5.5 L/kg), and sufentanyl (Vdss 4.9 L/kg), already widely distributed in the extravascular space, are theoretically less sensitive to these phenomena.

In terms of metabolic interactions, the clearance of midazolam, extensively metabolized by CYP3A4/5, is likely to be modified by CYP inhibitors or inducers. Thus, its exposure could be significantly increased by combining it with lopinavir/r [87]. As a result, the administration of high doses or prolonged infusions of midazolam to patients receiving lopinavir/r may cause long-lasting hypnotic effects, delayed recovery, and respiratory depression, requiring dose adjustment. Propofol presents little risk of metabolic interactions because its clearance depends on hepatic blood flow (and therefore little on intrinsic metabolic activity). The same is true for fentanyl, which, although metabolized by CYP 3A4, has a high hepatic extraction rate (0.7 to 0.8), making it insensitive to variations in the activity of metabolic enzymes. Cisatracurium is degraded by non-CYP P450-dependent pathways and its clearance is not particularly dependent on liver function.

Thus, similar to the volume of distribution, the clearance of certain drugs used in the ICU is probably more highly affected by the specific consequences of SARS-CoV-2 infection than by drug-drug interactions. As the clearance of propofol and fentanyl is highly dependent on hepatic blood flow, systemic exposure to these molecules could increase due to a reduction in hepatic blood flow in the event of circulatory insufficiency, frequently present in ARDS [88]. Finally, from a pharmacodynamic point of view, dexmedetomidine has bradycardizing effects that must be taken into account in patients receiving azithromycin and hydroxychloroquine, in whom the QT interval may increase.

CONCLUSION

Knowledge about COVID-19 infection continues to evolve. Several drugs have been proposed to treat the infection. However, they are sometimes used in patients who are treated chronically with other drugs or for whom a new treatment may become necessary. Co-administration of these drugs thus exposes such patients to a significant risk of drug-drug interactions. These can be anticipated by having good knowledge of the pharmacokinetic properties of the drugs and, notably, their metabolic pathways, as well as knowledge of their pharmacodynamics. Respect for the contra-indications and precautions for use, dosage adjustment, and close monitoring must be applied to allow the safe use of these drugs.

Of note, this paper is based on current data about the drugs proposed for the treatment of COVID-19. However, this is a rapidly evolving field and other drugs and substances are currently being evaluated.

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Table 1. Main drug-drug interactions with the drugs currently used in the context of COVID-19 infection requiring therapeutic intervention (TDM, drug dosage modification, or consideration of alternatives). The list is not exhaustive and is a selective list of the most important drug-drug interactions.

ECG: electrocardiogram, TDM: therapeutic drug monitoring, SSRI: selective serotonin reuptake inhibitor, SRI: serotonin reuptake inhibitor, BC: blood count, BID: bis in die, AUC: area under the curve of drug concentrations, Rauc: Ratio of AUCs (12)

Substrate	**Perpetrator**	**Interaction type**	**Potential risk**	**Degree of interaction**	**Action**
Antipyretics, antalgics					
Paracetamol	Favipiravir	Pharmacokinetic, increase in exposure	Increased risk of toxicity	Weak, AUC increase of about 15%.	Maximum dose 3g/d.
Tramadol	Lopinavir/r	Pharmacokinetic, change in tramadol and metabolite exposure	Modification of antalgic effect and side effects	Variable, depending on potential compensation between metabolic pathways	Surveillance
Codeine	Lopinavir/r	Pharmacokinetic,	Decrease in antalgic	Variable, according	Surveillance

		decrease in morphine exposure	effect	to effects on CYP2D6 and CYP3A4	
Oxycodone	Lopinavir/r	Pharmacokinetic, increase in oxycodone exposure	Increase in side effects	AUC increase from 160 to 300%	Surveillance
Morphine	Lopinavir/r	Pharmacokinetic, change in morphine and metabolite exposure	Modification of antalgic effect and side effects	Variable, depending on potential compensation between metabolic pathways	Surveillance
Drugs used in cardiovascular diseases					
Simvastatin	Lopinavir/r	Pharmacokinetic, increase in simvastatin exposure	Muscle cytolysis	Rauc = 25	Treatment discontinuation or switch to pravastatin
Felodipin	Lopinavir/r	Pharmacokinetic, increase in calcium-channel antagonist	Arrhythmia, hypotension	Rauc > 5	Switch to amlodipin every other day

		exposure			
Metoprolol	Lopinavir/r	Pharmacokinetic, increase in metoprolol exposure	Arrhythmia, hypotension	Rauc > 3	Switch to a beta-blocker with limited metabolism and identical pharmacodynamic profile
Eplerenone	Lopinavir/r	Pharmacokinetic, increase in eplerenone exposure	Hyperkaliemia, hypotension	Rauc > 4	Switch to spironolactone
Ivabradine	Lopinavir/r	Pharmacokinetic, increase in ivabradine exposure	Severe bradycardia	Rauc > 6	Consider a switch to atenolol in the absence of heart failure or a switch to amlodipin every other day
Drugs used in infectious diseases					
Azithromycin	Hydroxychloroquine	Pharmacodynamic	QT prolongation	+40 mSec in 30% of patients, > 500	Consider an alternative - Use

				mSec in 10% of patients	with caution with ECG monitoring
Hepatitis					
Sofosbuvir	Hydroxychloroquine	Pharmacodynamic	Cardiac rhythm disorders	Unknown	ECG and kaliemia monitoring
Glecaprevir/Pibrentasvir	Hydroxychloroquine	Pharmacokinetic, increase in hydroxychloroquine exposure	QT prolongation	Modest	ECG and kaliemia monitoring, TDM of hydroxychloroquine
Protease inhibitors (HIV and HVC)	Lopinavir/r	Pharmacokinetic, increase in drug exposure	Overdosage	High	Not recommended: consider an alternative
Tenofovir disoproxil	Lopinavir/r	Pharmacokinetic, increase in tenofovir exposure	Renal adverse events	AUC ↑ 30%	Monitor kidney function
Tenofovir	Remdesivir	Pharmacodynamic, Competition with metabolic pathway	Potential decrease in drug effect	Unknown	Evaluate the relevance of the association
HIV					

Rilpivirine	Lopinavir/r	Pharmacodynamic and pharmacokinetic	QT prolongation	Modest	ECG and kaliemia monitoring, TDM of rilpivirine
Rilpivirine	Hydroxychloroquine	Pharmacodynamic	QT prolongation	Unknown	ECG and kaliemia monitoring
Lopinavir/r	Nevirapine Efavirenz Etravirine	Pharmacokinetic, Decrease in lopinavir/r exposure	Decrease in drug effect	Cmin ↓ 40%	Not recommended
Hydroxychloroquine	Nevirapine Efavirenz Etravirine	Pharmacokinetic, Decrease in hydroxychloroquine exposure	Decrease in drug effect	Unknown	Not recommended
Maraviroc	Lopinavir/r	Pharmacokinetic, Decrease in maraviroc exposure	Orthostatic hypotension	AUC ↑ 400%	Decrease maraviroc dose to 150 mg BID and TDM of maraviroc
Tuberculosis					
Rifampicin	Hydroxychloroquine	Pharmacokinetic,	Decrease in drug	High	Not recommended -

		Decrease in hydroxychloroquine exposure	effect		Consider drug adjustment with TDM
Rifampicin	Lopinavir/r	Pharmacokinetic, Decrease in lopinavir/r exposure	Decrease in drug effect	High	Not recommended - Consider drug adjustment with TDM
Rifabutin	Hydroxychloroquine	Pharmacokinetic, Decrease in hydroxychloroquine exposure	Decrease in drug effect	Modest	TDM of hydroxychloroquine
Rifabutin	Lopinavir/r	Pharmacokinetic, Decrease in lopinavir/r exposure, Increase in rifabutin exposure	Decrease in drug effect	Rifabutin AUC increased by a factor of 5.7	Decrease rifabutin dose to 150 mg three times a week; TDM of lopinavir
Moxifloxacin, Bedaquiline, Delamanide	Hydroxychloroquine	Pharmacodynamic	QT prolongation	Unknown	ECG and kaliemia monitoring

Bedaquiline, Delamanide	Lopinavir/r	Pharmacokinetic, increase in tuberculosis drug exposure	QT prolongation	Modest	ECG and kaliemia monitoring, TDM of tuberculosis drugs
Ethambutol	Hydroxychloroquine	Pharmacodynamic, addition of adverse events	Ocular toxicity	Unknown	Retinopathy risk assessment
Amikacin	Remdesivir	Pharmacodynamic, addition of adverse events	Nephrotoxicity	Unknown	Monitor kidney function
Drugs used in organ transplantation and autoimmune diseases					
Tacrolimus	Lopinavir/r	Pharmacokinetic, increase in tacrolimus exposure	Nephrotoxicity	AUC increase up to 140 times	Consider 0.5 mg/week then adjust with TDM
Cyclosporine	Lopinavir/r	Pharmacokinetic, increase in cyclosporine exposure	Nephrotoxicity	Important	Consider 25 mg/d or every other day then adjust with TDM
m-TOR inhibitors	Lopinavi/r	Pharmacokinetic,	Overdosage	Important	Consider very low

		increase in m-TOR inhibitor exposure			dosage and ajust with TDM
Mycophenolic acid	Lopinavir/r	Pharmacokinetic, Enterohepatic recirculation inhibition	Low exposure to mycophenolic acid, graft rejection	AUC ↓ up to 60%	TDM of mycophenolic acid (AUC)
Calcineurin inhibitors	Hydroxychloroquine	Pharmacodynamic	QT prolongation	Unknown	ECG and kaliemia monitoring - TDM of calcineurin inhibitors and hydroxychloroquine
Calcineurin inhibitors, m-TOR inhibitors	Tocilizumab	Pharmacokinetic, decrease of cytokines, CYP downregulation mechanism	Decrease in immunosuppressive drug concentrations, Graft rejection	Unknown	Close immunosuppressive drug TDM
Drugs used in neuropsychiatric pathologies					
Citalopram, Escitalopram	Hydroxychloroquine	Pharmacodynamic	QT prolongation	7 to 10 ms	Discontinuation of SSRI or consider switch to

					an SRI with no torsade de pointes risk
Hydroxyzine	Hydroxychloroquine	Pharmacodynamic	QT prolongation	Unknown	Discontinuation of the drug or consider an alternative
Conventional antipsychotics	Hydroxychloroquine	Pharmacodynamic	QT prolongation	Unknown	Do not discontinue antipsychotic treatment but ensure close ECG monitoring
Clozapine	Smoking cessation	Pharmacokinetic	For hospitalizations of longer than 1 week, there is a risk of overdosage	Up to 2-fold increase in drug exposure	Decrease clozapine dose and monitor BC
Methadone	Smoking cessation	Pharmacokinetic	For hospitalization of longer than 1 week, there is a risk of overdosage	Unknown	Decrease methadone dose and monitor ECG

Cocaine	Hydroxychloroquine Azithromycin	Pharmacodynamic	QT prolongation	Unknown	Investigate drug use and monitor ECG
Ergotamine, Dihydroergotamine	Azithromycin	Pharmacokinetic	Distal necrosis (ergotism)	Unknown	Discontinuation of ergot alkaloids
Carbamazepine, Phenytoin, Phenobarbital	Lopinavir/r,	Pharmacokinetic	Decrease in lopinavir/r exposure	AUC ↓ 50%	No dose adjustment