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REVIEW ARTICLE

Pharmacokinetics/Pharmacodynamics of Antiviral Agents Used to Treat SARS-CoV-2 and Their Potential Interaction with Drugs and Other Supportive Measures: A Comprehensive Review by the PK/PD of Anti-Infectives Study Group of the European Society of Antimicrobial Agents

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Abstract

There is an urgent need to identify optimal antiviral therapies for COVID-19 caused by SARS-CoV-2. We have conducted a rapid and comprehensive review of relevant pharmacological evidence, focusing on (1) the pharmacokinetics (PK) of potential antiviral therapies; (2) coronavirus-specific pharmacodynamics (PD); (3) PK and PD interactions between proposed combination therapies; (4) pharmacology of major supportive therapies; and (5) anticipated drug–drug interactions (DDIs). We found promising in vitro evidence for remdesivir, (hydroxy)chloroquine and favipiravir against SARS-CoV-2; potential clinical benefit in SARS-CoV-2 with remdesivir, the combination of lopinavir/ritonavir (LPV/r) plus ribavirin; and strong evidence for LPV/r plus ribavirin against Middle East Respiratory Syndrome (MERS) for post-exposure prophylaxis in healthcare workers. Despite these emerging data, robust controlled clinical trials assessing patient-centred outcomes remain imperative and clinical data have already reduced expectations with regard to some drugs. Any therapy should be used with caution in the light of potential drug interactions and the uncertainty of optimal doses for treating mild versus serious infections.

Key Points

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) PK/PD Study Group has especially convened a group of clinical and PK/PD experts to provide guidance for all relevant drug therapies for infections caused by the SARS-COV-2 virus. The underlying presents guidance at a high level of detail on the key pharmacokinetic/pharmacodynamic characteristics of drugs at the current most commonly used antiviral regimens, clinically significant drug–drug interactions, and the effect of extracorporeal therapies (e.g. renal replacement therapy, extracorporeal membrane oxygenation) on dosing requirements.

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1 Drugs Active Against SARS-CoV-2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic on 11 March 2020 and has triggered enormous, unrelenting and ever-increasing demands on health systems in countries globally. The number of patients infected with this novel coronavirus escalated dramatically, with the first clinical trial for a vaccine initiated in the US on 16 March 2020. There has been an unprecedented and immediate need to define and optimize treatment for infected patients. However, the evidence for therapies against SARS-CoV-2 is inadequate, leading many medical teams to prescribe drugs based on mechanistic data with limited clinical data supporting their activity. This lack of knowledge is also manifest in highly variable doses or proposed duration of therapy for treatment. It is also noteworthy that many drugs are not uniformly available throughout the world; a therapeutic option for COVID-19 in one country may not be available in another. Inevitably, this heterogeneity of practice and accessibility may lead to patients receiving suboptimal therapy because of a lack of appropriate and readily available data for drugs that are obtainable in a particular country.

Coronaviruses commonly cause infection in non-human animal hosts, and therefore animal models might be informative to investigate drugs that may be applicable for use in humans. Along with preclinical data from animal models, there are emerging reports from in vitro cell culture models that provide information on the mechanism of action and antiviral effects of tested compounds [1]. Application of in silico modeling and simulation techniques can then advance infection model-defined exposure targets to identify doses appropriate for human use. While this process provides highly valuable direction for antiviral therapeutic selection when there is an emergent need for such drugs, these methods are analogous to those applied in the drug development process. The clinical utility of preclinically validated dosing regimens relies heavily on the available pharmacokinetic (PK) data used in the simulation process for the particular drug. That is, PK data obtained from healthy volunteers rather than the population of interest (i.e. severely ill patients with acute respiratory distress syndrome [ARDS]) may not be applicable due to differences in bioavailability for orally or subcutaneously administered drugs, and alterations in the drug's volume of distribution (Vd) and clearance (CL) that may result in sub- or supratherapeutic exposure; therefore careful interpretation for clinical use is essential [2]

Therapeutic agents available for COVID-19 can introduce other treatment challenges, particularly drug interactions. Various compounds that have been proposed for the treatment of SARS-CoV-2 are affected by the cytochrome P450 (CYP)-metabolizing system as either substrates, enzyme inhibitors or enzyme inducers, and consideration of these interactions on dosing requirements of concomitant SARS-CoV-2 or other supportive drug therapies is essential. For instance, lopinavir/ritonavir (LPV/r) combination has strong inhibitory effects on CYP3A4 and CYP2D6, which also metabolize hydroxychloroquine (another probable agent active against SARS-CoV-2), which may result in an increase in potential toxic effects such as Torsades de pointes [3].

With the significant uncertainty regarding the choice and dose of drug therapy for patients with active COVID-19 disease, there is a clear need for a review of potential treatments and interpretation of dosing considerations to optimize treatment based on current evidence. The aim of this narrative review is to summarize available literature to guide treatment choices in clinical trials, and to inform local and national policymakers to enable clinicians to optimize the treatment regimens for patients outside trials with SARS-CoV-2 infection.

2 Search Methodology

Literature regarding the treatment of SARS-CoV-2 is highly dynamic and evolving. Many results have not yet been published in their final form. In order to allow for a fast evaluation of the most relevant treatment practices at hospitals worldwide, the PK/PD of Anti-Infective Study Group (EPASG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) established rapid communication by social media channels. In addition, the World Health Organization website was evaluated for reports pertinent to our review, including preprints [4]

Once the drugs of interest were identified (Table 1) their PK/pharmacodynamic (PK/PD) characteristics were summarized (Table 2). Subsequently, we searched databases to identify single and combination therapies being evaluated in clinical trials. Searches of the PubMed and Embase databases (no date limits) were then performed using the search strategy '(drug name) AND (coronavirus)' to identify clinical trials, retrospective clinical studies, and animal or in vitro studies on the drug therapies (Table 3). In addition, information on drug–drug interactions (DDIs) was extracted [5]. Teams of at least three authors extracted and agreed upon data presented in each table. We deliberately excluded analysis of combinations with remdesivir since the currently open trials investigate only monotherapy.

Because COVID-19 requires intensive care treatment in up to 10% of infected patients, electronic supplementary Table 1 presents the most commonly used supportive drugs, while electronic supplementary Table 2 presents the potential interactions of these drugs with antivirals. Unless specifically stated, the Summary of Product characteristics

(SmPC) or package leaflets of medications have been used as the basis for the assessment of DDIs. These interactions are also constantly updated on online platforms, such as the COVID-19 drug interaction webpage maintained by the University of Liverpool [3]. Extracorporeal support treatments might also be necessary for critically ill patients with COVID-19 and, as such, in Table 4 we describe the influence of extracorporeal support treatments on antiviral PK.

3 List of experimental antiviral agents explored for treatment of Covid 19

3.1 Antiviral Agents for the Treatment of COVID-19

Table 1 contains general information about the key drugs currently suggested for the treatment of COVID-19. Most agents were originally approved for the treatment of other viral infections. The exception is (hydroxy)chloroquine, an immunomodulatory drug with known antiviral activity that has been used for over 60 years, primarily to treat malaria and, more recently, autoimmune diseases, such as systemic lupus erythematosus and inflammatory arthritis. Some of the agents listed have been studied with related viruses, such as Middle East Respiratory Syndrome (MERS) coronavirus. Most agents discussed in this article purportedly have direct mechanisms of action against SARS-CoV-2. As COVID-19 disease has emerged only recently, drugs currently being used are in various phases of clinical trials and none are approved for use in COVID-19, except for the very recent approval of remdesivir. The dosing regimens are based on current knowledge, derived from other indications, and may change in the future when new data become available. Dosing regimens in children are unavailable for most agents. In general, the heterogeneous total daily doses for drugs against COVID-19 disease are similar to, or greater than, that used for other indications.

3.2 Pharmacokinetics/Pharmacodynamics (PK/PD) of Antiviral Agents for the Treatment of COVID-19

Table 2 summarizes the data on the PK/PD properties of the agents recommended for SARS-CoV-2 and other viruses. The available data are limited and are based primarily on in vitro studies in various cell lines. Drug potency is usually presented as the half maximal effective concentration (EC_{50}), which varies between viruses. The EC_{50} values for other viruses are compared against SARS-CoV-2, with a lower EC_{50} indicating increased potency. While EC_{90} is usually preferred as a therapeutic target for antivirals, it can only be inferred from EC_{50} when the Hill coefficient is 1 (in which case EC_{90} is ninefold higher than EC_{50}). Since the Hill coefficient is not routinely reported, we used EC_{50} to compare the relative potencies of the antivirals reviewed.

Data on other coronaviruses have been summarized; however, where data are unavailable for coronaviruses, other pathogens are reported. For chloroquine and PegIFN-α2β, measured intracellular concentrations are correlated with the in vitro EC_{50} and, as such, serve as the PK/PD index [6, 7]; however, there are no studies comparing various PK/PD indices for these agents.

The EC_{50} values for remdesivir, chloroquine, and ribavirin against SARS-CoV-2 were compared with those of MERS. For both remdesivir and ribavirin, the EC_{50} values were higher than for MERS, indicating that a larger dose may be needed to treat COVID-19. The EC_{50} value of chloroquine was within the same range for SARS-CoV-2 and MERS. In an in vitro study, Yao et al. compared chloroquine with hydroxychloroquine and reported that hydroxychloroquine was more potent than chloroquine [7], although caution interpreting these results is warranted since different EC_{50} values were reported depending on whether experiments were conducted for 24 or 48 h. Since EC_{50} is not a time-dependent parameter, this calls into question how reliable the estimate is and how well it may translate to an in vivo target. In addition, this study has recently undergone a critical review by authors from the US FDA [8]. Furthermore, other studies have conversely found chloroquine to be more potent than hydroxychloroquine [9], and emerging data from randomized controlled trials (RCTs) [10] and large observational studies [11] suggest that both chloroquine and hydroxychloroquine result in increased mortality when used in COVID-19. While we include chloroquine and hydroxychloroquine in the summary of evidence, there is great uncertainty as to the clinical role of these drugs in hospitalized COVID-19 patients. Indeed, meanwhile, several negative studies have led to discontinuation of the use of these two drugs in many clinical studies in many countries [12, 13], yet other countries still continue to use these widely available drugs due to a lack of alternatives.

Several interferons (IFNs), including IFN-α, PegIFN-α2β, IFN-α1β and IFN-β1β, have been examined for the treatment of COVID-19; however, they are administered as adjuvant therapy with other anti-COVID-19 drugs.

The currently available data on drug efficacy and PK/PD targets for COVID-19 are inadequate to support therapeutic drug monitoring; however, some data on plasma concentrations are available in the literature (Table 2). When drug concentrations are available in the literature, it may be prudent to evaluate individual concentrations in patients in which high variability in PK combined with an increased likelihood of DDIs and adverse effects can be expected, i.e. typically critically ill patients.

A shortcoming of the data presented in Table 2 is the fact that the total concentrations of the drug were reported by

Table 1 Antivirals and supportive drugs used to treat COVID-19

Substance generic name	Normal approved indication	Studied virus	Study phase for COVID-19	Antiviral mode of action	Supplier/ major countries where available	Currently used dose for approved indication (mg)	Adult dosing in COVID-19 (mg)	Child dosing in COVID-19 (mg)	Route of administration	Route of elimination
Remdesivir	Antiviral under investigation; FDA emergency use authorization to COVID-19	COVID-19, MERS-CoV, SARS-CoV, HCoV-229E, HCoV-OC43	Phase III/IV (NCT04292899; NCT04292730; NCT04280705; NCT04321616; NCT04315948)	Viral RNA polymerase inhibitor	Gilead® Europe USA	200 mg on day 1, followed by 100 mg/day (total 10–14 days)	200 mg on day 1 followed by 100 mg/day on days 2–10	WT < 40 kg: 5 mg/kg load, then 2.5 mg/kg/24 h WT ≥ 40 kg: 200 mg load, then 100 mg/24 h [39]	IV	NA
Chloroquine	Approved antimalarial; FDA emergency use authorization to COVID-19	COVID-19, SARS-CoV, HCoV-OC43	Cell cultures/co-cultures Phase III/IV (NCT04362332; NCT04331600; NCT04351191)	Inhibition of endosome-mediated viral entry, and pH-dependent steps in viral replication [40]	Sanofi-Aventis® Global	100 mg/24 h	600 mg/12 h on day 1, followed by 300 mg bid on days 2–5; alternative: 500 mg/12 h over 5 days [7]	NA	PO or IV	50% renal clearance (excreted unchanged in the urine); metabolized by CYP2C8, CYP3A4 and, to lesser extent, CYP2D6
Lopinavir/ritonavir	Approved antiviral	COVID-19, MERS-CoV	Phase IV	HIV protease inhibitor/boost of other protease inhibitors	Abbott® Global	400 mg/12 h + 100 mg/12 h	LPV/r 400/100 mg/12 h PO, 14 days [37]	(a) Age 14 days–12 months: 16 mg/4 mg (LPV/r)/kg/12 h (b) Age 12 months–18 years: (i) WT < 15 kg: 13 mg/3.25 mg (LPV/r)/kg/12 h; (ii) WT ≥ 15 to 40 kg: 11 mg/2.75 mg (LPV/r)/kg/12 h [41]	PO	LPV: metabolized by CYP3A Ritonavir: CYP3A4 and, to a lesser extent, CYP2D6 [42]

Table 1 (continued)

Substance generic name	Normal approved indication	Studied virus	Study phase for COVID-19	Antiviral mode of action	Supplier/ major countries where available	Currently used dose for approved indication (mg)	Adult dosing in COVID-19 (mg)	Child dosing in COVID-19 (mg)	Route of administration	Route of elimination
Favipiravir	Approved antiviral	COVID-19	Phase III (NCT04349241; NCT04356495; NCT04303299; NCT04373733; NCT04351295; NCT04361461; NCT04345419)	Viral RNA polymerase inhibitor	Fujifilm Toyama Chemical® China, Japan	1600 mg/12 h on day 1 then 600 mg/12 h on days 2–5	Under study	NA	PO; IV under development [43]	Genetic variant in digestive transport (Pgp; ABCB1) and metabolism (aldehyde oxydase) to an inactive M1, urinary excretion; both metabolized by and inhibited by aldehyde oxidase [43]
Ribavirin	Approved antiviral	COVID-19	Cell cultures/co-cultures; phase II (NCT04276688)	Unclear: multiple possible mechanisms	Generic Europe	400–600 mg/12 h	500 mg/12 h or 500 mg/8 h IV [44]	NA	Aerosol, PO or IV	Renal clearance (30%), some fecal excretion
Arbidol/ Umifenovir	Approved antiviral	COVID-19	Phase IV (NCT04350684; NCT04260594; NCT04286503)	Inhibits membrane fusion, stimulation of the immune system	Russian Research Chemical Pharmaceutical Institute Russia, China	50–200 mg/6 h	200 mg/8 h [44]	Safety unclear [45]	PO	Via the feces, metabolized in hepatic and intestinal microsomes (33 metabolites known), CYP3A4 [46]

Table 1 (continued)

Substance generic name	Normal approved indication	Studied virus	Study phase for COVID-19	Antiviral mode of action	Supplier/ major countries where available	Currently used dose for approved indication (mg)	Adult dosing in COVID-19 (mg)	Child dosing in COVID-19 (mg)	Route of administration	Route of elimination
Hydroxychloroquine	Approved antimalarial; FDA emergency use authorization to COVID-19	COVID-19	Phase III/IV (NCT04261517; NCT04362332; NCT04334967; NCT04359615; NCT04316377)	Inhibition of endosome-mediated viral entry, and pH-dependent steps in viral replication [40]	Sanofi-Aventis® Europe	100 mg/24 h	400 mg/day for 5 days (NCT04261517) PO 400 mg/12 h on day 1 followed by 200 mg/12 h on days 2–5 [7]	NA	PO	50% renal clearance (excreted unchanged in the urine); metabolized by CYP2C8, CYP3A4, and, to lesser extent, CYP2D6
PegIFN-α2β	Approved antiviral	COVID-19, MERS-CoV, HCoV	Phase IV (NCT04254874; NCT04291729)	Adjuvant treatment: enhancement of phagocytic/ cytotoxic mechanisms	– Europe	1.5 µg/kg/week SC	45–50 µg/12 h (NCT04254874;NCT04291729)	NA	Nebulized; SC	Renal clearance [47]
IFN-α1β	Approved antiviral	COVID-19, MERS-CoV, HCoV	Early phase I (NCT04293887)	Adjuvant treatment: enhancement of phagocytic/ cytotoxic mechanisms	– China	–	10 µg/12 h (NCT04293887)	NA	Nebulized	Renal clearance [47]

Table 1 (continued)

Substance generic name	Normal approved indication	Studied virus	Study phase for COVID-19	Antiviral mode of action	Supplier/ major countries where available	Currently used dose for approved indication (mg)	Adult dosing in COVID-19 (mg)	Child dosing in COVID-19 (mg)	Route of administration	Route of elimination
IFN-α	Approved antiviral	COVID-19, MERS-CoV, HCoV	Not applicable (NCT04251871) [48]	Adjuvant treatment: enhancement of phagocytic/ cytotoxic mechanisms	– China	–	5 million IU/12 h (NCT04251871) [48]	IFN-α 200,000–400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water, nebulization two times per day for 5–7 days [45]	Nebulized	Renal clearance [47]
IFN-β1β	Approved antiviral	COVID-19, MERS-CoV, HCoV	Phase II (NCT04276688)	Adjuvant treatment: enhancement of phagocytic/ cytotoxic mechanisms	– Europe, China	25 μg SC injection alternate day	25 μg SC injection alternate day for 3 days (NCT04276688)		SC	Renal clearance [47]
Camostat	Approved for chronic pancreatitis	COVID-19, MERS-CoV, SARS-CoV	Phase I/II/III (NCT04353284; NCT04321096; NCT04374019; NCT04355052)	Blocks interaction between the S1 protein and the SARS-CoV-2 target cell	Nichi Iko Japan	200 mg/8 h	200 mg/12 h or 8 h	NA	PO	Renal clearence [49]

Table 1 (continued)

Substance generic name	Normal approved indication	Studied virus	Study phase for COVID-19	Antiviral mode of action	Supplier/ major countries where available	Currently used dose for approved indication (mg)	Adult dosing in COVID-19 (mg)	Child dosing in COVID-19 (mg)	Route of administration	Route of elimination
Nafamostat	Approved for pancreatitis	COVID-19, MERS-CoV, SARS-CoV	Phase II (NCT04352400)	Blocks the interaction between the S1 protein and the SARS-CoV-2 target cell	Nichi Iko Japan	20–50 mg IV (prophylaxis of pancreatitis) [50]	NA	NA	IV	Renal clearence [51]

Unclear: Multiple possible mechanisms

COVID-19 Coronavirus disease 2019, *MERS-CoV* Middle East Respiratory Syndrome coronavirus, *SARS-CoV* severe acute respiratory syndrome coronavirus 2, *HCoV-229E* human coronavirus 229E, *HCoV-OC43* human coronaviruses subtype OC43, *RNA* ribonucleic acid, *IV* intravenously, *NA* not available, *PO* orally, *LPV/r* lopinavir/ritonavir, *PgP* permeability glycoprotein, *Unclear* multiple possible mechanisms, *bid* twice daily, *CYP* cytochrome P450, *WT* weight, *SC* subcutaneously, *IFN* interferon, *HIV* human immunodeficiency virus

the majority of papers, or information as to whether total or free concentrations were reported is not available at all. This must be taken into account when PK/PD calculations are performed, since, unusually, only the free fraction will be active.

3.3 Combination SARS-CoV-2 Antiviral Agents and Associated Drug–Drug Interactions

As there are no approved COVID-19 therapies, combination therapy against SARS-CoV-2 with agents exhibiting different modes of action may have a role in helping to optimize therapy until clinical trial data become available. This combination approach is consistent with the management of many viral, fungal, and bacterial infections where there are suboptimal single-agent treatment options. We aimed to assess the evidence of repurposed antiviral combinations that were not specifically designed to treat SARS-CoV-2.

The strongest RCT evidence exists for remdesivir, which has been shown to reduce the recovery time for moderate–severe COVID-19 in comparison with standard care (11 vs. 15 days [14]; $p < 0.001$). These data have now led some to declare remdesivir to be the standard of care for COVID-19 disease, even though there was no significant difference in mortality between the remdesivir and standard care groups.

Other, albeit less-compelling, data exist for LPV/r plus ribavirin therapy (retrospective, case–control study) resulting in a reduction in mortality, acute respiratory distress syndrome (ARDS), and viral shedding in the treatment of SARS (Table 3). However, extrapolating these data to SARS-CoV-2 should be undertaken with caution as LPV/r and another HIV protease inhibitor, nelfinavir, exhibit good activity against SARS [15, 16] but are less effective against MERS [17]. Another potential combination includes LPV/r, ribavirin and IFN (prospective, non-randomized, comparative controlled study), resulting in shorter duration of viral shedding and hospital stay when compared with LPV/r alone. Randomized trials involving these drugs, based on their promising in vitro activity, will provide important guidance. Of note, we warn against the use of hydroxychloroquine in combination with other drugs that may prolong the QT interval due to potentially life-threatening adverse effects [11]. In a large cohort study, all patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, but concurrent treatment with azithromycin was associated with greater changes in QTc [18]. However, since combinations of QTc-prolonging drugs do not necessarily result in additive QTc prolongation, a case-by-case evaluation seems warranted [19].

Table 2 PK/PD of antivirals and other drugs used to treat COVID-19

Drug	PD metric (e.g. IC_{50})	Type of study used for COVID-19 experiments	EC_{50}/EC_{90} for COVID-19 (μM)	EC_{50}/EC_{90} for other indications	Blood concentrations
Remdesivir	EC_{50}	In vitro (vero E6 cells)	0.77 [53] 23.15 [54]	0.09 μM (MERS-CoV) in a mice model [55]	10 μM in nonhuman primates was reached after a dose of 10 mg/kg IV [56]
	EC_{90}	In vitro (vero E6 cells)	1.76 [53]	NA	Note: treatment outcomes were no different from control patients hospitalized with COVID-19 [57]
Chloroquine	EC_{50}	In vitro (vero E6 cells)	1.13–7.36 [7, 9, 53]	0.05 μM (*Plasmodium vivax*) in vitro [58] 3.1 μM (HIV) in vitro [59] 3.0 μM (MERS-CoV) in vitro [60] 4.1 μM (SARS-CoV) in vitro [60]	A concentration of 6.9 μM is achievable in patients after a 500 mg dose [53, 61]; however, concentrations as low as 0.5–1.0 μM were also demonstrated after a 300 mg/12 h regimen (unpublished Data, Bruggemann on file). Note: higher adverse effects and lethality were found in patients with COVID-19 who received 600 mg/12 h for 10 days compared with 450 mg/12 h on day 1 and once daily between days 2 and 5 [10] and higher mortality in hospitalized patients [10, 11]
	EC_{90}	In vitro (vero E6 cells)	6.9 [53]	0.358 μM (*P. vivax*) in vitro at 30 h [58]	
Lopinavir/ritonavir	EC_{50}	In vitro (vero E6 cells)	LPV: 26.63 [54]	LPV: 8–11.6 μM (MERS-CoV) in mice/vitro [55, 60] LPV: 17.1 μM (SARS-CoV) in vitro [60] Ritonavir: 24.9 μM (MERS-CoV) in a mice model [55] LPV/r: 8.5 μM (MERS-CoV) in a mice model [55]	LPV C_{max} values average 12.72 μM (with p2.5 of 6.36 μM to p97.5 of 23.85 μM) and ritonavir C_{max} values average 0.7 μM (with p2.5 of 0.2 μM to p97.5 of 2.22 μM) [62]. Note: treatment outcomes were no different from standard of care in hospitalized patients with COVID-19 [37]. LPV/r combined with ribarivin and interferon-β1β demonstrated better clinical and virological response than LPV/r alone in patients with mild to moderate disease [63]
Favipiravir	IC_{50}	In vitro (vero E6 cells)	61.88 [53] >100 [54]	67 μM for Ebola [64]	Concentrations of 1190 ± 478 μM were achieved 1 h after a favipiravir 400 mg loading dose in nonhuman primates [65]. Median total trough (predose) and average concentrations of 360 and 520 μM, respectively, following 1200 mg/12 h with a loading dose of 6000 mg in Ebola-infected patients [66], with a fall in average concentration on day 4. Nonlinear PK Note: faster viral clearance and radiological improvement was reported in patients who received favipiravir when compared with LPV/r [67]

Table 2 (continued)

Drug	PD metric (e.g. IC_{50})	Type of study used for COVID-19 experiments	EC_{50}/EC_{90} for COVID-19 (μM)	EC_{50}/EC_{90} for other indications	Blood concentrations
Ribavirin	EC_{50}	In vitro (vero E6 cells)	109.50 [53] > 100 [54]	40.94 ± 12.17 μM (MERS-CoV) in vitro [17]	Concentration range between 25.0 and 10.65 μM achieved with a ribavirin dose regimen of 400–600 mg/12 h [68]
Arbidol (Umifenovir)	EC_{50}	In vitro (vero E6 cells)	4.11 uM (3.55–4.73) [69]	24.72 μM (Avian infectious bronchitis virus as representative for Coronaviridae) [70]	Concentrations of 1.47, 2.60 and 4.53 μM achieved after 0.2, 0.4 and 0.8 g doses, respectively [71] Note: treatment outcomes were reported to be no different from standard of care (symptomatic and supportive treatment) in hospitalized patients with COVID-19 in a retrospective cohort [72]
Hydroxychloroquine	EC_{50}	In vitro (vero E6 cells)	0.72 μM [7] (outlying value) 4.51–12.96 [9]		Concentration > 1.49 μM (> 500 ng/ml) achievable following a 6 mg/kg/day dosing regimen [73] Note: treatment outcomes were no different from control patients hospitalized with COVID-19 [12], and observational data show increased mortality [11]
	Concentration shown to reduce viral titers			80 μM (Zika virus) in vitro [74]	
PegIFN-α2β	EC_{50}	NA	NA	0.04 μg/L (HCV patients) [6]	C_{max} of 0.53 μg/L in patients after 1.5 μg/kg SC [75]
IFN-β1β	EC_{50}	NA	NA	17.64 ± 1.09 UI/ml (MERS-CoV) [17], 1.37 U/ml (MERS-CoV) [76]	Concentration of 240 UI/ml following 8 million IU SC [77]
IFN-β1β	EC_{90}	NA	NA	38.8 U/ml (MERS-CoV) [76]	
Camostat	EC_{50}	In vitro (Calu-3 cells)	0.087–1 [78, 79]	0.198–1 uM (SARS-CoV) [78, 79] 0.444 uM (MERS-CoV) [79]	Concentration of 589 uM was achieved 12 h after Camostat 40 mg IV administration in humans [49]
	EC_{90}	In vitro (Calu-3 cells)	5 [78]	5 uM (SARS-CoV; MERS-CoV) [78]	
Nafamostat	EC_{50}	In vitro (Calu-3 cells)	0.005 [79]	0.0059 uM (MERS-CoV) [79] 0.0014 uM (SARS-CoV) [79]	Concentrations of 41, 116 and 174 uM after doses of 10, 20 and 40 IV, respectively [80]

PD pharmacodynamic, *PK* pharmacokinetic, IC_{50} half maximal inhibitory concentration, *COVID-19* coronavirus disease 2019, EC_{50} half maximal effective concentration, EC_{90} 90% effective concentration, *MERS-CoV* Middle East Respiratory Syndrome coronavirus, *NA* not available, *HIV* human immunodeficiency virus, *SARS-CoV* severe acute respiratory syndrome coronavirus 1, *LPV/r* lopinavir/ritonavir, *IFN* interferon, *HCV* hepatitis C virus, *SC* subcutaneously, *PegIFN* pegylated interferon, *IV* intravenously, C_{max} maximum concentration

Table 3 Drug–drug interactions of proposed antiviral combinations against coronavirus

Proposed combination (with clinical trial reference if available)	Pharmacodynamic rationale	Drug–drug interactions with level of severity and therapeutic advice [81]	Level of evidence: 1. Clinical trial in coronavirus 2. Retrospective clinical data 3. In vivo animal or in vitro data
Ribavirin + LPV/r [82]	Inhibition of replication PLUS inhibition of RNA synthesis	Increased risk of liver toxicity Level of severity: major Therapeutic advice: monitor for increased liver toxicity	1. Clinical trials: No data 2. Retrospective clinical data : (a) Retrospective matched cohort study for SARS-CoV infection: 41 cases treated with LPV/r + ribavirin vs. 111 historical controls treated with ribavirin alone; better clinical outcome (ARDS and death) at day 21 after onset of symptoms: 2.4% vs. 28.8%; $p < 0.001$. No difference in outcome reported for early vs. delayed treatment [15] (b) Multicenter retrospective matched cohort study for SARS-CoV infection: 75 cases treated with LPV/r + ribavirin vs. 977 controls treated with ribavirin. Reduction in death (2.3% vs. 15.6%; $p < 0.05$) and intubation (0% vs. 11%; $p < 0.05$) was evident only in the subgroup of initial treatment with LPV/r; no significant difference in the late treatment group [38] (c) MERS-CoV infection: post-exposure prophylaxis with ribavirin + LPV/r in 43 healthcare workers resulted in a 40% reduction in the risk of MERS-CoV infection, with no severe adverse events during treatment [83] 3. In vivo animal or in vitro data: In vitro checkerboard assay for synergy on SARS-CoV demonstrated inhibition of the cytopathic effect with a concentration of LPV of 1 μg/ml with ribavirin 6.25 μg/ml when the viral inoculum was < 50 median tissue culture infectious dose [15, 84]
LPV/r + Arbidol [82]	Inhibition of replication PLUS inhibition of RNA synthesis PLUS inhibition of viral entry	No clinical data available CYP3A4 is major pathway of metabolism for arbidol; strong inhibition of CYP3A4-mediated metabolism of arbidol by ritonavir is plausible Level of severity: Unknown Therapeutic advice: Monitor for increased toxicity of arbidol [70]	1. Clinical trials: No data 2. Retrospective clinical data: Case series ($n = 4$) of mild or severe COVID-19 pneumonia successfully treated with LPV/r + arbidol + Shufeng Jiedo Capsule (traditional Chinese medicine) [85, 86] 3. In vivo animal or in vitro data: No data

Table 3 (continued)

Proposed combination (with clinical trial reference if available)	Pharmacodynamic rationale	Drug–drug interactions with level of severity and therapeutic advice [81]	Level of evidence: 1. Clinical trial in coronavirus 2. Retrospective clinical data 3. In vivo animal or in vitro data
Chloroquine + LPV/r	Inhibition of replication PLUS inhibition of viral entry	Increased risk of QTc prolongation (potentially dangerous interaction) Inhibition of CYP3A-mediated metabolism of chloroquine by ritonavir Level of severity: Major Therapeutic advice: Monitor ECG and monitor for increased toxicity of chloroquine if used in combination. Dose reduction of chloroquine might be necessary in case of severe toxicity	1. Clinical trials: No data, but ongoing open-label study currently being undertaken in China (ChiCTR2000029741) [87] 2. Retrospective clinical data: No data 3. In vivo animal or in vitro data: No data
Emtricitabine + tenofovir (Truvada)	Inhibition of RNA synthesis (dual therapy)	No data	1. Clinical trials: No data 2. Retrospective clinical data: No data 3. In vivo animal or in vitro data: No data
Favipiravir + interferon	Inhibition RNA synthesis PLUS immune modulation	No data	1. Clinical trials: Open-label, nonrandomized, comparative controlled study in 80 patients with SARS-CoV-2 infection. Thirty-five patients were treated with FPV plus inhaled IFN-α. Forty-five historic controls received LPV/r plus inhaled IFN-α. Treatment with FPV/IFN led to shorter viral clearance time and improvement in chest imaging at D14. Fewer adverse events were found in the FPV/IFN arm [67] 2. Retrospective clinical data: No data 3. In vivo animal or in vitro data: No data
Emtricitabine + tenofovir (Truvada) + LPV/r [88]	Inhibition of replication PLUS inhibition of RNA synthesis	Increased tenofovir absorption (i.e. 32% AUC increase; 51% C_{min} increase) through P-glycoprotein inhibition Level of severity: Moderate Therapeutic advice: Monitor for tenofovir-associated toxicity	1. Clinical trials: No data 2. Retrospective clinical data: No data 3. In vivo animal or in vitro data: No data

Table 3 (continued)

Proposed combination (with clinical trial reference if available)	Pharmacodynamic rationale	Drug–drug interactions with level of severity and therapeutic advice [81]	Level of evidence: 1. Clinical trial in coronavirus 2. Retrospective clinical data 3. In vivo animal or in vitro data
Interferon + ribavirin	Immune modulation PLUS inhibition of RNA synthesis	No data	1. Clinical trials: Ongoing open-label, single-center, prospective, randomized controlled clinical trial in China comparing LPV/r plus IFN-α vs. ribavirin plus IFN-α, vs. LPV/r plus IFN-α plus ribavirin [89] 2. Retrospective clinical data: (a) Multicenter observational study in critically ill patients with MERS-CoV infection. Of 349 MERS-CoV-infected patients, 144 received RBV/rIFN (rIFN-α2a, rIFN-α2b or rIFN-ß1a). Treatment was not associated with a reduction in 90-day mortality or faster MERS-CoV RNA clearance [90] b. Retrospective cohort study of patients with MERS-CoV requiring ventilation support who received supportive care ($n = 24$) vs. oral ribavirin + pegylated IFN-α2a ($n = 20$). Treatment with ribavirin + IFN-α2a was associated with significantly improved survival at 14 days, but not at 28 days [91] 3. In vivo animal or in vitro data: Synergistic antiviral effect between ribavirin and type I IFN (i.e. IFN-α [84, 92] or IFN-ß [84, 92, 93]) on SARS-CoV was described in two studies performed in human and Vero cell lines
LPV/r + interferon + ribavirin	Immune modulation PLUS inhibition of RNA synthesis PLUS inhibition of replication	Level of severity: Major Therapeutic advice: Monitor for increased risk for hepatotoxicity (for combination protease inhibitor + ribavirin and protease inhibitor + interferon)	1. Clinical trials: One open-label, randomized, multicenter, phase II trial in Hong Kong in 127 patients with confirmed SARS-CoV2 infection. Eighty-six patients received LPV/r + interferon-β1b + ribavirin combination treatment, and 41 received LPV/r alone. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab, and shorter duration of hospitalization than the control group [63] Ongoing open-label, single-center, prospective, randomized controlled clinical trial in China comparing LPV/r plus IFN-α vs. ribavirin plus IFN-α, vs. LPV/r plus IFN-α plus ribavirin [89] 2. Retrospective clinical data: Two case reports, one patient recovered, one patient died during hospital stay due to septic shock [94, 95] 3. In vivo animal or in vitro data: No data

Table 3 (continued)

Proposed combination (with clinical trial reference if available)	Pharmacodynamic rationale	Drug–drug interactions with level of severity and therapeutic advice [81]	Level of evidence: 1. Clinical trial in coronavirus 2. Retrospective clinical data 3. In vivo animal or in vitro data
Hydroxychloroquine + azithromycin	Immune modulation PLUS inhibition of viral entry	Increased risk of QTc prolongation (potentially dangerous interaction) Level of severity: Major Therapeutic advice: Monitor ECG	1. Clinical trials: One open-label, non-randomized clinical study in 36 patients with confirmed SARS-CoV2 infection (interim analysis of ongoing trial) [96]. Of 36 patients, 14 received hydroxychloroquine treatment, 6 received hydroxychloroquine/azithromycin combination treatment and 16 were controls. The proportion of patients with negative PCR in nasopharyngeal samples was significantly higher in hydroxychloroquine-treated patients at days 3–6 post-inclusion vs. control patients. If hydroxychloroquine was used in combination with azithromycin, the proportion of patients with negative PCR in nasopharyngeal samples was significantly higher on days 3–6 when compared with patients treated with hydroxychloroquine monotherapy. One open-label, non-randomized clinical study in 80 patients with confirmed SARS-CoV2 infection [97]. Of 80 patients, all expect 2 improved clinically. A rapid fall in nasopharyngeal viral load was observed, with 83% negative at day 7, and 93% at day 8 2. Retrospective clinical data: One retrospective cohort study of 1438 patients hospitalized for COVID-19 in 25 hospitals in metropolitan New York. 735 patients received hydroxychloroquine + azithromycin, 211 received azithromycin alone, 271 received hydroxychloroquine alone, and 221 received neither drug [98] There we no differences in hospital mortality between different treatments One retrospective study of 1061 confirmed SARS-CoV2 patients treated with hydroxychloroquine + azithromycin for at least 3 days in Marseille, France. Good clinical and virological cure was obtained in 973 (91.7%) patients within 10 days [99] Retrospective electronic case record review of 96,032 hospitalized patients. Multivariable Cox proportional hazard model with matched case–control analysis found hydroxychloroquine plus a macrolide resulted in 23.8% mortality vs. 9.3% in controls. Significantly higher mortality was seen with hydroxychloroquine, or chloroquine alone and chloroquine plus macrolide vs. control [11] 3. In vivo animal or in vitro data: No effect of hydroxychloroquine, with or without azithromycin, on viral load in either treatment or prophylaxis in a non-human primate model [100]

LPV/r lopinavir/ritonavir, *AUC* area under the curve, *COVID-19* coronavirus disease 2019, *SARS-CoV* severe acute respiratory syndrome coronavirus, *MERS-CoV* Middle East Respiratory Syndrome coronavirus, *ARDS* acute respiratory disease syndrome, *QTc* corrected QT interval, *ECG* electrocardiogram, C_{min} trough concentration, *RNA* ribonucleic acid, *RBV/rIFN* ribavirin + recombinant IFN, *PCR* polymerase chain reaction, *FPV* favipiravir, *IFN* interferon, *CYP* cytochrome P450, *LPV/r* lopinavir/ritonavir

3.4 Most Commonly Used Supportive Agents (Intensive Care Unit, Pain, Fever, Anticoagulation)

Supportive care with other pharmacological agents, including antibiotics, sedatives, analgesics, and anticoagulants, need to be considered when treating with antiviral and other repurposed agents, particularly in the critical care setting. Electronic supplementary Table 1 lists the major drugs by class and highlights potential interactions. In particular, caution should be exercised for CYP3A4 DDIs with narrow therapeutic index drugs, such as anticoagulants (warfarin, acenokumarol, dabigatran, rivaroxaban, and apixaban) and immunosuppressant agents in transplant recipients in whom additional monitoring may be required. For patients sedated with midazolam, dose reduction should be considered when patients are treated with CYP3A4 inhibitors, such as LPV/r, as there is a significant risk of oversedation, resulting in unnecessary prolongation of intensive care unit (ICU) stay [20]. There are multiple potential interactions resulting in cardiac complications, including prolonged QT interval with (hydroxy)chloroquine combinations and LPV/r, that necessitate monitoring. As these DDI are substantial, the balance of risk versus benefit should be carefully considered prior to drug administration to prevent significant morbidities.

According to a preliminary report in patients hospitalized with COVID-19, dexamethasone significantly reduced 28-day mortality among those patients receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support [21]. If these data hold true, at the moment corticosteroids belong to the most active intervention in patients with severe COVID-19 disease. In this aspect, it should also be noted that while dexamethasone is a potent inductor of CYP3A4 induction, this effect seems to be less relevant for the common alternative, betamethasone [22].

3.5 Interaction Between Antivirals and Supportive Drugs

The potential interactions for most drugs used to treat COVID-19, and comedications, are provided in detail in electronic supplementary Table 2. It is emphasized that not all described interactions are necessarily clinically relevant, and the ultimate decision on the need for avoiding a certain combination or dose adjustment must be taken by the treating physician.

DDIs are an important consideration for all therapies used to treat COVID-19. This is especially the case with repurposed antiretroviral drugs and (hydroxy)chloroquine, which have many potential DDIs. Clinicians treating patients infected with SARS-CoV-2 need to carefully consider the potential for DDIs before commencing therapy. Many DDIs may be mitigated by simple measures such as continuous electrocardiogram (ECG) monitoring or by having maximum allowable QT intervals (e.g. 450 ms) for the interacting combinations to be used. The ritonavir component of LPV/r is deliberately used to inhibit CYP3A4 and thereby increase antiretroviral drug concentrations; however, this leads to a significant potential to increase concentrations of other coadministered therapies that are CYP3A4 substrates. Notably, the interaction between (hydroxy)chloroquine and other agents that may inhibit drug CL can result in cardiac toxicity and patients should be monitored closely. Based on the long half-life of (hydroxy)chloroquine (in the magnitude of several weeks), interactions might persist for several days after treatment has ceased. This may be especially problematic in critically ill patients with pre-existing cardiovascular morbidity, and extreme caution should be observed. The use of triazole antifungals should be avoided or carefully monitored if administered concurrently with LPV/r due to DDIs. Potential DDIs are reported between either LPV/r and important drugs commonly used in the critical care setting, including ketamine, rocuronium, and many of the opioid agents. Utmost care is required when considering the coadministration of these agents with antiretroviral drugs in critically ill patients. The newer investigational antiviral agents, remdesivir and favipiravir, appear to have a lower potential for DDIs; however, the main concern with their use is decreased concentrations if coadministered with enzyme inducers. (Hydroxy)chloroquine may prolong the QT interval, therefore ECG monitoring is required when they are coadministered with other agents known to cause QT interval prolongation. Coadministration of (hydroxy)chloroquine with drugs that are known to prolong the QT interval, such as amiodarone and flecanide, is not recommended. However, clinical experience with these drugs is much less than the repurposed antiretrovirals. A comprehensive and evolving DDI database has been created by the University of Liverpool and this should be consulted for potential DDIs not covered in our review [3].

3.6 The Effect of Extracorporeal Treatments on the PK of COVID-19 Therapies

Systemic inflammatory response syndrome (SIRS) may occur with the use of extracorporeal treatments, and may cause alterations in CYP-mediated metabolism. SIRS increases activity of all CYPs, except CYP3A4, which decreases. In children, CYP enzymes are commonly immature in neonates and take time to reach similar activity levels as adults [23]. In this section, as well as in Table 4, we summarize the principles of PK alterations that occur with extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT) to impact drug exposure and thereby dose. Although limited studies have been conducted

Table 4 Expected PK of the antivirals used to treat COVID-19 with extracorporeal support treatments

Name of antiviral	Effects on pharmacokinetic parameters			Protein binding (%)
	RRT	ECMO	Extracorporeal systemic inflammatory response[a]	
Remdesivir	NA	NA	NA	NA
Chloroquine	–	Likely[b]	Alterations in cytochrome metabolism	40–60 [25, 31]
Lopinavir	–	Likely[b]	Alterations in cytochrome metabolism	98–99 [101]
Ritonavir	–	Likely[b]	Alterations in cytochrome metabolism	99 [102]
Favipiravir	–	Increases Vd	Alterations in cytochrome metabolism	54 [32]
Ribavirin	–	Increases Vd	–	0 [26]
Arbidol (Umifenovir)	–	–	Alterations in cytochrome metabolism	NA
Hydroxychloroquine	–	Likely[b]	Alterations in cytochrome metabolism	40–60 [25, 31]
PegIFN-α2β	–	–	–	NA
IFN-α1β	–	–	–	NA
IFN-α	–	–	–	NA

RRT renal replacement therapies, *ECMO* extracorporeal membrane oxygenation, *NA* not available, *Vd* volume of distribution, *IFN* interferon

[a]For example, systemic inflammatory response syndrome (SIRS) caused by extracorporeal life support system

[b]Sequestration of drug to the ECMO oxygenator is likely, but is unlikely to affect dosing needs

on COVID-19 therapies, optimized dosing should consider these potential impacts on individual patients.

3.7 The Impact of Extracorporeal Membrane Oxygenation

The most common mechanisms by which ECMO is likely to affect the PK of drugs are sequestration by the oxygenator and tubing in the ECMO circuit, leading to reduced circulating drug concentrations [23]. While lipophilic drugs and highly protein-bound drugs are more likely to be sequestered in the circuit, hydrophilic drugs can be significantly affected by hemodilution and changes in albumin concentration, potentially leading to altered protein binding and an increased Vd. Indeed, an increased free fraction means more distribution from the central compartment into the peripheral compartments (i.e. tissues), leading to an increased apparent Vd [24]

3.8 The Impact of Renal Replacement Therapy

Sepsis-related acute kidney injury often develops in the context of multiple organ dysfunction syndrome and leads to relevant modifications of several PK parameters. Moreover, high volumes of fluid resuscitation, commonly required in critically ill patients [25], may significantly affect the Vd of several drugs [26]. When Vd of a drug is typically small since the drug is mostly retained in the intravascular compartment (where protein binding is high), clinically significant removal of small drugs by RRT is unlikely. Where Vd is < 1.0 L/kg and protein binding is not high (> 80%), the commencement of RRT adds further complexities for dosing, with possible extracorporeal CL. Renally excreted drugs are usually affected by RRT to a much greater extent than hepatically excreted drugs [27]. Only the free (i.e. unbound) drug is cleared across the RRT filter. With the exception of a few drugs, the molecular weight (MW) of the most commonly used antimicrobial agents is lower than 1000 Da and plays a key role, especially in diffusive RRT modalities, as the sieving coefficient (SC) of a molecule is inversely proportional to MW. The SC is generally similar for drugs with a MW around 1000–1500 Da in convective modalities. However, in diffusive techniques, the ratio of dialysate to plasma solute concentration (saturation coefficient [SA]) is more strictly dependent on MW and tends to decrease progressively as MW increases [28]. Whereas intermittent hemodialysis (IHD) or continuous venovenous hemodialysis (CVVHD) are essentially diffusive techniques, continuous venovenous hemofiltration (CVVH) is a convective technique, and continuous venovenous hemodiafiltration (CVVHDF) is a combination of both. As a general rule, the efficiency of drug removal by the different techniques is expected to be CVVHDF > CVVH > CVVHD/IHD, but this can still vary greatly depending on the physicochemical properties of each drug and the CRRT settings [29]. Dialyzer membrane characteristics (cut-off) may also play a key role.

3.9 PK Data of Drugs Active Against SARS-CoV-2

Table 4 extrapolates basic drug physicochemistry and known PK data to predict the likely effects of ECMO on PK. Sparse data on the IHD CL of (hydroxy)chloroquine are available and suggest that the high Vd of (hydroxy)chloroquine limits significant alteration in drug concentrations [30]. As such, ECMO is predicted to have minimal impact on the drug

concentrations of (hydroxy)chloroquine, although sequestration onto the oxygenator and circuit tubing cannot be excluded. There is also the hypothesis that (hydroxy)chloroquine rapidly partitions intracellularly, potentially resulting in minor effects overall and in the vascular compartment [25]. The PK of LPV/r in hemodialysis suggests that dosing adjustments are unnecessary in treatment-naive patients, in part due to the high protein binding of these drugs [31]. CVVH has no clinically relevant contribution to total CL of favipiravir [32]. For ribavirin, CL was reduced by 50% via IHD [33], which is not considered significant enough to justify increasing the dose based on increases in dialysate or RRT filtration flow rate [34]. No significant effect of RRT on IFN concentrations is predicted due to the MW of the IFN compounds which usually exceeds 15 kDa [35, 36].

4 Discussion

We have provided an in-depth rapid review on the preclinical and clinical antiviral treatment options for SARS-CoV-2. It should be emphasized that although the approach in the current review is pragmatic to allow for real-time assessment of international practice, it cannot guarantee that all experimental combinations have been captured. However, the therapeutic investigations for COVID-19 are highly dynamic and almost daily new treatment options are empirically tested in clinical practice globally. More importantly, the quality of data regarding the safe and effective use of treatment options are generally poor and strong recommendations cannot be provided regarding the superiority of one treatment or combination over another. It is clear with absolute certainty that robust controlled clinical trials are imperative. Such studies must use either clinical endpoints (demonstrating a benefit in how the patient feels, functions, or survives) or improving meaningful biomarker performance such as time of viral shedding. Regarding the study design, randomization, blinding, and an appropriate control (either a comparator that has been proven effective or placebo) are recommended. Meanwhile, all antiviral therapies should be used with caution due to the significant drug interactions, risk for adverse events, and the need to evaluate optimal doses for treating mild versus serious infections.

All drugs presented in Table 1 should be seen as possible treatment options for patients with, or very likely to develop, a critical COVID-19 disease despite no strong recommendations being available. We found that PK/PD indices indicate that many of the currently used treatment regimens fail to achieve sufficient concentrations when EC_{50} values are compared with plasma PK, which might partially explain limited clinical success of these combinations. Before investigation of any new combination empirically, PK/PD models with Monte Carlo simulations should be used to predict success and, wherever possible, integrate an adaptive design to also account for tolerability. Failure to develop these models might lead to suboptimal drug exposure in patients, resulting in erroneous omission of therapeutic options before exploring their full potential.

Relevant DDIs exist both between combinations of antivirals and between antivirals and supportive therapies. Since many of the combinations have not been widely used in the ICU, healthcare providers should be alerted to closely monitor for DDIs. With the omnipresent work overload related to the COVID-19 crisis within hospitals and ICUs, applications (apps) or programs should be developed to support real-time clinical decisions and dose adaption.

A recent study of LPV/r showed no effect against SARS-CoV-2 [37] but this conclusion should be interpreted with caution. Only 199 patients were randomized and the non-significant trend showed a 5.8% decrease in mortality with LPV/r versus no treatment. If this is the true effect size, a larger sample size is required. Furthermore, the high overall mortality reported in this study suggests that these patients had severe disease, and the late initiation of therapy (i.e. within 12 days after the onset of symptoms) may have affected the results. As such, the clinical benefit of early initiation of LPV/r monotherapy should be further investigated. The clinical trials of SARS or MERS evaluated LPV/r in combination with ribavirin, rather than as monotherapy. Lopinavir and ribavirin have been found to be synergistic in vitro against SARS [15], and, more importantly, the combination of LPV/r and ribavirin reduced mortality and viral shedding when compared with historical controls [15]. Another study in SARS reported that early initiation of combination therapy consisting of LPV/r plus ribavirin, compared with historical controls treated with ribavirin alone, significantly reduced mortality and the need for ventilation; notably, there was no effect with delayed or late therapy [38]. Extrapolating these data to SARS-CoV-2 should be taken with caution since LPV and the protease inhibitor nelfinavir appears to exhibit good activity against SARS [16] but is less effective against MERS [17]. Nonetheless, LPV/r, ribavirin and IFN combinations should be investigated for in vitro synergy against SARS-CoV-2, and considered for clinical evaluation if the results are promising. One open-label RCT comparing LPV/r plus inhaled IFN-β plus ribavirin against LPV/r in SARS-CoV-2-positive patients reported a significantly shorter time from start of treatment to negative nasopharyngeal swab, and shorter duration of hospitalization, when compared with the control group. Of note, we advise against the use of combinations of hydroxychloroquine with azithromycin due to emerging safety issues with this drug combination, in particular increased risk for QTc prolongation [18].

In summary, there are promising therapeutic options for COVID-19 in the absence of a vaccine at present. The

encouraging RCT results for remdesivir provide some direction for the treatment of COVID-19 patients and has led to positive evaluation of the drug for severe forms of COVID-19 by the European Medicines Agency and the FDA. Further to this, it is highly likely that one or more other agents mentioned in this review, or, more plausibly, a combination, may emerge as a prophylactic or early treatment option with the potential to decrease viral shedding and transmission and/or reduce disease progression to the requirement of ventilatory support.

From a PK/PD perspective, the development should not only focus on the discovery of new treatment options but should also investigate common key aspects of treatment, particularly the following.

- When is the optimal time point to start antiviral therapy, what is the required duration, and when is it too late to initiate treatment?
- In line with the open questions regarding dexamethasone, when is it time to start anti-inflammatory drugs and which biomarkers can we use to tailor this therapy?
- What role can the individualization of therapy based on dose adaption and therapeutic drug monitoring (TDM) play in the treatment of COVID-19?

Meanwhile, due to the lack of highly effective and sufficiently evaluated treatment options, the most important strategy currently is avoidance of infection by the implementation of optimal public health measures that incorporate appropriate handwashing and social distancing. Furthermore, the use of rapid diagnostic tests to identify silent carriers, along with active disease, and the availability of personal protective equipment to protect from transmission, are critical to limit the massive spread of infection. Lastly, the development of vaccines (in which a clinical trial has been initiated in the US) is vital to immediately protect individual immunity and our global community long-term.

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Compliance with Ethical Standards

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