

## Drug interactions: a review of the unseen danger of experimental COVID-19 therapies

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As global health services respond to the coronavirus pandemic, many prescribers are turning to experimental drugs. This review aims to assess the risk of drug–drug interactions in the severely ill COVID-19 patient. Experimental therapies were identified by searching ClinicalTrials.gov for ‘COVID-19’, ‘2019-nCoV’, ‘2019 novel coronavirus’ and ‘SARS-CoV-2’. The last search was performed on 30 June 2020. Herbal medicines, blood-derived products and *in vitro* studies were excluded. We identified comorbidities by searching PubMed for the MeSH terms ‘COVID-19’, ‘Comorbidity’ and ‘Epidemiological Factors’. Potential drug–drug interactions were evaluated according to known pharmacokinetics, overlapping toxicities and QT risk. Drug–drug interactions were graded GREEN and YELLOW: no clinically significant interaction; AMBER: caution; RED: serious risk. A total of 2378 records were retrieved from ClinicalTrials.gov, which yielded 249 drugs that met inclusion criteria. Thirteen primary compounds were screened against 512 comedications. A full database of these interactions is available at [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org). Experimental therapies for COVID-19 present a risk of drug–drug interactions, with lopinavir/ritonavir (10% RED, 41% AMBER; mainly a perpetrator of pharmacokinetic interactions but also risk of QT prolongation particularly when given with concomitant drugs that can prolong QT), chloroquine and hydroxychloroquine (both 7% RED and 27% AMBER, victims of some interactions due to metabolic profile but also perpetrators of QT prolongation) posing the greatest risk. With management, these risks can be mitigated. We have published a drug–drug interaction resource to facilitate medication review for the critically ill patient.

### Introduction

‘Desperate times call for desperate remedies’. But what if experimental treatments for COVID-19 have a risk of causing harm in the very group of individuals most in need of such therapies? And what if most of these harms remain unrecognized? Drug–drug interactions (DDIs) involving two or more drugs have long been recognized as having the potential to cause harm. *In vitro* data, clinical studies in healthy volunteers, and patients (usually evaluating the magnitude of change in drug exposure in the blood stream), and expert interpretation are the main tools to point to the likelihood of a clinically significant DDI. However, it is important to recognize that for patients with multiple morbidities who may have organ dysfunction there is a real risk of increased susceptibility to adverse effects and therefore the same DDI may be more likely to result in harm. People requiring experimental COVID-19 therapies will often be clinically unstable, and the development of toxicities from DDIs may easily be misattributed.

Since 1998, the University of Liverpool has established a prescribing resource for managing DDIs in individuals receiving antiretroviral therapy to treat or prevent HIV.<sup>1</sup> The database contains a review of over 31000 drug interactions, synthesized from data systematically collected from medical and scientific literature, plus information from drug regulatory authorities or expert opinion. Mirroring the principles of GRADE,<sup>2</sup> drug interaction assessments are based on predetermined criteria, with critical evaluation of the quality of evidence. The Liverpool methodology is published<sup>3</sup> and has been used in the review process for national and international treatment guidelines (e.g. WHO<sup>4</sup>, BHIVA<sup>5</sup>). A similar DDI resource was developed for hepatology<sup>6</sup> in 2011, and, together with Radboudumc, Nijmegen, the Netherlands, for cancer<sup>7</sup> in 2018. In March 2020, we published a DDI resource for experimental COVID therapies ([www.covid19-druginteractions.org](http://www.covid19-druginteractions.org)). This review summarizes the methodology and processes undertaken to establish the resource.

## Why is this review needed?

Use of experimental COVID-19 therapies is rapidly evolving, and steadily increasing. Whilst initial use was in the sickest individuals (who are also most likely to have multiple comorbidities and polypharmacy), wider deployment as prophylaxis (e.g. to frontline health workers) is being considered.<sup>8-10</sup> Several of these experimental therapies have the propensity for DDIs that may cause clinical harms. A review of the potential for interactions with drugs used for common comorbidities, or frequently used in the intensive care setting is urgently needed. Resulting knowledge will be collated, curated, and made readily available to support prescribers as an online resource on [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org).

## Methods

### Identifying experimental therapies

Experimental therapies for COVID-19 were identified by searching ClinicalTrials.gov using the following search terms: 'COVID-19', '2019-nCoV', '2019 novel coronavirus' and 'SARS-CoV-2'. The last search was run on 30 June 2020. Experimental therapies were selected for inclusion as a primary drug for DDI analysis on the following basis: (i) use for treatment or prevention of COVID-19; (ii) use in randomized controlled trials that are multi-country, or multi-centre within one country; (iii) widespread use outside of randomized trials if listed as options to consider from national bodies and specialist societies. Our evaluation panel comprising senior/principal pharmacists, academic pharmacologists and an infectious diseases specialist (C.M., F.M., A.B., D. Back, D. Burger and S.K.) discussed potential inclusion for all candidates identified. We excluded compounds where only *in vitro* data were available, as well as blood-derived products such as serum from recovered patients, and herbal and traditional medicines.

### Identifying comedications

We utilized a semi-systematic approach to selection of drug classes to include as comedications. Briefly, we first gathered evidence on the frequency and type of comorbidities reported in individuals with severe COVID-19 disease (using MeSH terms 'COVID-19' [supplementary concept], 'Comorbidity' and 'Epidemiological Factors'). We then identified commonly used classes of compounds for these comorbidities from UK treatment guidelines (e.g. NICE).<sup>11</sup> Within each therapeutic class, we then selected a list of drugs that were most frequently used across Europe and North America (we have previously made this selection based on country guidelines and the input of our International Editorial Board for HIV).

In addition to high-frequency comorbidities in severe COVID-19 patients, we also selected comedications likely to be used in disease management as well as those associated with high-consequence DDIs. These included drugs used in anaesthetics and intensive care, drugs used for treating symptoms or complications of COVID-19, and commonly used narrow therapeutic index drugs.

### Evaluation of potential DDIs

DDIs were identified as previously described by Seden *et al.*<sup>3</sup> Briefly, data on the clinical pharmacology of experimental therapies were extracted from approved product labels, published submissions to regulatory authorities in Europe, USA and Japan,<sup>12-23</sup> published case reports or studies and, where none of the above were available, from personal communication with the manufacturer. Propensity for a drug interaction was based on screening against known pathways for absorption, distribution, metabolism and excretion of all drugs involved. This included potential for induction and inhibition of enzymes and transporters, interactions affecting bioavailability, protein binding and hepatic/renal excretion. Additional considerations

included overlapping toxicities and potential interactions involving drugs with a narrow therapeutic index (e.g. anti-arrhythmics, anti-coagulants). A significantly increased risk of QT prolongation as a result of combining two drugs with known risk of torsade de pointes<sup>24</sup> or else a drug interaction leading to elevated concentrations of a drug with known risk of torsade or QT prolongation were separately coded.

Details of how drug interaction evaluations are made with regard to strength of recommendation and quality of evidence underpinning that recommendation have been previously published,<sup>24</sup> and were undertaken by our evaluation panel (see above).

For our COVID-19 recommendations we also took the following additional considerations into account when assessing drug interactions: (i) the likely critical condition of any patient requiring these therapies; (ii) the relatively short duration of coadministration; (iii) the incremental risks to health workers from additional monitoring; (iv) available, safer alternatives; and (v) the option of pausing the comedication whilst COVID-19 therapy is administered.

Interactions were graded into four levels: GREEN, no clinically significant interaction expected; YELLOW, potential interaction likely of weak intensity, additional action/monitoring or dosage adjustment unlikely to be required; AMBER, potential interaction that may require close monitoring, alteration of drug dosage or timing of administration; RED, these drugs should not be co-administered. The decision to give or withhold drugs is always the responsibility of the prescriber. A pragmatic use of our DDI recommendations is to regard GREEN and YELLOW flags as an indication that no clinically significant DDIs exist, while RED flags indicate significant cause for concern. An AMBER flag does not preclude co-administration (since DDIs can usually be managed or monitored) but rather indicates the need to consider risks and benefits in that individual patient for whom treatment is considered.

The DDI grading of the antiretroviral drug lopinavir/ritonavir is mostly similar between the COVID-19 and the HIV websites except for contraceptives or antidepressants devoid of QT risk. The DDI has been downgraded on the COVID-19 site given the short treatment course, which makes monitoring or dose adjustment of these therapeutic agents unnecessary. Another DDI grading difference relates to strong enzyme inducers (e.g. carbamazepine, phenytoin, St John's Wort) which are contraindicated in the COVID-19 website with drugs metabolized by cytochrome P450, given the risk of treatment failure and difficulty of managing the DDI.

## Results

### Experimental COVID-19 therapies

As a new and evolving pandemic, it is unsurprising that little consensus has been reached between national and international guidelines and specialist societies surrounding the use and choice of experimental therapies, and the number of potential therapeutic compounds is rapidly increasing.<sup>25-33</sup> Therefore, our range of experimental therapies will necessarily be expanded over the coming weeks and months.

As of 30 June 2020, a total of 2378 clinical trials were retrieved from ClinicalTrials.gov. Two hundred and forty-nine drugs from ClinicalTrials.gov met our inclusion criteria. The drugs listed included 27 antivirals, 48 immunotherapy drugs, 5 antimalarial drugs, 6 glucocorticoids and 163 miscellaneous compounds with different modes of action.

After selection for inclusion as a primary drug for DDI analysis based on the criteria above, the following 13 drugs were taken forward for analysis of DDIs: anakinra, baricitinib, chloroquine, favipiravir hydroxychloroquine, interferon  $\beta$ , lopinavir/ritonavir,

nitazoxanide, remdesivir, ribavirin, ruxolitinib, sarilumab and tocilizumab. We did not include azithromycin in this review, as the reasons for giving this drug appeared to be in part for use in preventing bacterial superinfection rather than as a true adjuvant. Dexamethasone, which has recently been shown in the RECOVERY trial to reduce 28 day mortality in patients hospitalized with COVID-19 receiving invasive mechanical ventilation or oxygen,

was excluded from this review but added to the COVID drug interactions site on 15 July 2020.<sup>34</sup>

### DDI potential of COVID-19 therapies

Table 1 summarizes the key interaction information for each experimental therapy. A comprehensive breakdown of interaction

**Table 1.** Drug interaction risk of experimental COVID-19 therapies

Experimental therapy	Interaction potential
Anakinra	No effect on CYP450 <i>per se</i> but anakinra reverses interleukin-induced suppression of cytochromes (e.g. IL-1 elevation during inflammation). Currently no <i>a priori</i> adjustment of CYP substrates needed. No effect on QTc. <sup>41</sup>
Baricitinib	Partially metabolized by CYP3A4 and a substrate for OAT3, P-gp, BCRP, and MATE2-K. May inhibit OCT1. Strong inhibitors of inducers of CYP3A4 are unlikely to significantly alter baricitinib exposure. Transporter inhibitors, with the exception of OAT3 inhibitors, are unlikely to cause a significant effect on baricitinib exposure. No effect on QTc. <sup>42</sup>
Chloroquine	A moderate inhibitor of CYP2D6 and P-gp and caution may be required when co-administering comedications metabolized or transported by these pathways with a narrow therapeutic index. Shown to prolong QTc and is on the known risk of TdP list. <sup>24</sup>
Favipiravir	Metabolized mainly by aldehyde oxidase (AO). Based on metabolism and clearance, clinically significant drug interactions are minimal. It does inhibit CYP2C8 and caution is required in combination with comedications metabolized by this route and AO. The QT prolongation risk is considered to be low. <sup>22,43</sup>
Hydroxychloroquine	A moderate inhibitor of CYP2D6 and P-gp and caution may be required when co-administering comedications metabolized or transported by these pathways with a narrow therapeutic index. Shown to prolong QTc and is on the known risk of TdP list. <sup>24</sup>
Interferon-β	Drug interaction potential not fully evaluated. May reduce the activity of CYP enzymes but the clinical significance is likely to be small. No effect on QTc. <sup>44</sup>
Lopinavir/ritonavir	Inhibits CYP3A as well as some key transporters: P-gp, BCRP and OATP1B1. Many drug interactions of clinical importance due to <b>increased</b> exposure of comedications using these pathways. Also, potential to <b>decrease</b> exposure of some drugs metabolized by other CYP enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19) and glucuronidation. Known to cause QT prolongation and is on the possible risk of TdP list. <sup>24</sup>
Nitazoxanide	Rapidly hydrolysed to tizoxanide; <i>in vitro</i> studies indicate nitazoxanide is unlikely to inhibit cytochromes. Tizoxanide is highly protein-bound (>99%), so caution is indicated when give with other highly protein-bound drugs with narrow therapeutic indices. No effect on QTc. <sup>45,46</sup>
Remdesivir	A prodrug predominantly metabolized by hydrolase activity. Based on rapid distribution, metabolism and clearance after IV administration, the likelihood of clinically significant interactions is low. No effect on QTc. <sup>23</sup>
Ribavirin	There is minimal potential for CYP450 or transporter-based interactions. No effect on QTc. <sup>15</sup>
Ruxolitinib	Metabolized by CYP3A4 and CYP2C9, ruxolitinib has the potential to be a victim of DDIs perpetrated by inhibitors or inducers of these enzymes. Ruxolitinib may inhibit BCRP and P-gp and caution is indicated with co-administering with substrates of these transporters with narrow therapeutic indices. <sup>47</sup>
Sarilumab	No effect on CYP450 <i>per se</i> but sarilumab reverses interleukin-induced suppression of cytochromes (e.g. IL-6 elevation during inflammation). Currently no <i>a priori</i> adjustment of CYP substrates needed. No effect on QTc. <sup>48</sup>
Tocilizumab	No effect on CYP450 <i>per se</i> but tocilizumab reverses interleukin-induced suppression of cytochromes (e.g. IL-6 elevation during inflammation). Currently no <i>a priori</i> adjustment of CYP substrates needed. No effect on QTc. <sup>18</sup>

BCRP, breast cancer resistance protein; CYP, cytochrome P450; MATE, multidrug and toxic compound extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; QTc, corrected QT interval; TdP torsades des pointes.

(a) Antiviral experimental COVID-19 drugs

	CLQ	FAVI	HCLQ	IFN- $\beta$	LPV/r	NTZ	RDV	RBV
Acenocoumarol	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↓ <sub>4<sup>49, 50</sup></sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Apixaban	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>3<sup>51</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Argatroban	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Aspirin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Betrixaban	↑♥ <sub>4</sub>	↔ <sub>4</sub>	↑♥ <sub>4</sub>	↔ <sub>4</sub>	↑♥ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Clopidogrel	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↓ <sub>3<sup>52-55</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Dabigatran	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↔ or ↓ <sub>2<sup>56</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Dalteparin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Dipyridamole	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↓ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Edoxaban	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Eltrombopag	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↓ 17% <sub>3<sup>57</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Enoxaparin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Fondaparinux	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Heparin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Phenprocoumon	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↑↓ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Prasugrel	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4<sup>54, 58</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Rivaroxaban	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4<sup>59</sup></sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Streptokinase	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Ticagrelor	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Tinzaparin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>
Warfarin	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↔ <sub>4</sub>	↓ <sub>4<sup>36, 60, 61</sup></sub>	↑ <sub>4</sub>	↔ <sub>4</sub>	↓ <sub>4<sup>62, 63</sup></sub>

**Figure 1.** Predicted DDIs between anti-coagulant, anti-platelet and fibrinolytic drug therapies and (a) antiviral experimental COVID-19 drugs or (b) anti-inflammatory experimental COVID-19 drugs. GREEN shading indicates no clinically relevant interaction; YELLOW shading indicates potential weak interaction; AMBER shading indicates potential interaction which may require dose modification or monitoring; RED shading indicates do not co-administer. Arrows indicate the potential for increased, decreased or unchanged exposure of the comedication (solid arrows) or experimental therapy (open arrows). The heart symbol (♥) indicates that these drugs have been identified by www.CredibleMeds.org as having a risk of QT prolongation and/or torsades des pointes. The risk may be concentration- or dose-related and/or additive if two or more such drugs are combined. Note, please check product labels for any additional cardiac warnings. Quality of evidence for PK interactions was assessed according to the principles of GRADE. Grades are High (1), Moderate (2), Low (3) and Very Low (4) as previously described by Seden *et al.*<sup>3</sup> CLQ, chloroquine; FAVI, favipiravir; HCLQ, hydroxychloroquine; IFN- $\beta$  interferon; LPV/r, lopinavir/ritonavir; NTZ, nitazoxanide; RDV, remdesivir; RBV, ribavirin.

potential and references are given in Table S1 (available as [Supplementary data](#) at JAC Online).

One main source of risk is inhibition of CYP3A4 by lopinavir/ritonavir (perpetrator). Given that ritonavir irreversibly inhibits CYP3A4, the inhibitory effect may last up to 5 days after stopping ritonavir.<sup>35</sup> On the other hand, lopinavir/ritonavir induces CYP1A2, CYP2C9, CYP2C19 and glucuronidation. Increase in CYP activity has been observed even after short-course treatment with lopinavir/ritonavir.<sup>36</sup> The resolution of the inducing

effect can take up to 3 weeks. Thus, monitoring of narrow therapeutic index drugs is warranted during and after stopping treatment with lopinavir/ritonavir. COVID-19 drugs are also potential victims of a DDI when co-administered with strong cytochrome P450 (CYP) inducers, as are chloroquine, hydroxychloroquine and remdesivir. DDIs with involvement of P-glycoprotein (P-gp) may also have clinical relevance as both chloroquine and hydroxychloroquine are moderate P-gp inhibitors.

## (b) Anti-inflammatory experimental COVID-19 drugs

	Anakinra	Baricitinib	Ruxolitinib	Sarilumab	Tocilizumab
Acenocoumarol	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Apixaban	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Argatroban	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Aspirin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Betrixaban	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Clopidogrel	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Dabigatran	↔ 4	↔ 4	↑ 4	↔ 4	↔ 4
Dalteparin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Dipyridamole	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Edoxaban	↔ 4	↔ 4	↑ 4	↔ 4	↔ 4
Eltrombopag	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Enoxaparin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Fondaparinux	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Heparin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Phenprocoumon	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Prasugrel	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Rivaroxaban	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Streptokinase	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Ticagrelor	↓ 4	↔ 4	↑ 4	↓ 4	↓ 4
Tinzaparin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Warfarin	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4

Figure 1. Continued

In addition to DDIs that have a pharmacokinetic (PK) basis (i.e. a change in drug exposure), pharmacodynamic DDIs can also be relevant, in particular because chloroquine, hydroxychloroquine and lopinavir/ritonavir can cause QTc prolongation, and combined use with other drugs that prolong the QTc should be avoided.

The most frequent comorbidities in patients with severe COVID-19 are hypertension, cardiovascular and cerebrovascular disease, diabetes, malignancy, gastrointestinal disease and respiratory system disease.<sup>37–40</sup> By including the different classes of treatments for each of these morbidities, and selecting other medicines used to support critical care or manage symptoms of COVID-19 disease, we identified a total of 512 comedications to screen against experimental COVID-19 therapies.

A full database of our DDI recommendations is posted on [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org). This website is continuously updated

as more comedications and further therapies for COVID-19 are added. Interactions between experimental COVID-19 drugs and comedications may be searched, but not interactions between comedications. The interaction checker focuses on PK interactions, but also warns for overlapping toxicity. Possible physicochemical interactions occurring in an infusion or syringe have not been addressed. We have also published prescribing resources advising how to administer experimental therapies in the case of swallowing difficulties, and renal or hepatic insufficiency. Examples of recommendations with the anticoagulant, antiplatelet and fibrinolytic class, antidiabetic class and antibiotic class can be seen in Figure 1.

As of 30 June 2020, a total of 512 comedications were screened against the 13 primary compounds. The numbers (frequencies) of RED and AMBER flags for experimental agents were as follows: anakinra 8 (2%) and 9 (2%), respectively; baricitinib, 7 (1%) and 12



(2%); chloroquine, 35 (7%) and 138 (27%); favipiravir, 0 (0%) and 14 (3%); hydroxychloroquine, 35 (7%) and 138 (27%); interferon- $\beta$ , 1 (0%) and 13 (3%); lopinavir/ritonavir, 52 (10%) and 209 (41%); nitazoxanide, 0 (0%) and 4 (1%); remdesivir, 9 (2%) and 0 (0%); ribavirin, 2 (0%) and 16 (3%); ruxolitinib, 7 (1%) and 66 (13%); sarilumab, 7 (1%) and 9 (2%); and tocilizumab, 7 (1%) and 9 (2%).

## Discussion

Experimental COVID-19 therapies carry significant risk for DDIs. Amongst these treatments, drug interactions involving the HIV protease inhibitor lopinavir/ritonavir were the most frequent, followed by chloroquine, hydroxychloroquine and ruxolitinib, with anakinra, baricitinib, favipiravir, interferon- $\beta$ , nitazoxanide, ribavirin, remdesivir, sarilumab and tocilizumab having low propensity for drug interactions.

Assessing the likelihood of a drug interaction is not always straightforward. Whilst the magnitude of change in exposure of either or both drugs can be quantified through a clinical study, the clinical relevance may vary according to the therapeutic index of the affected compound. Pharmacodynamic interactions (including overlapping toxicities) can be equally complex to judge, as in the case of drugs that cause QT prolongation, and which may also have exposures increased by a drug interaction. Regulatory authorities in the USA and EU may consequently differ in evaluation of risk and recommendations, e.g. with boosted protease inhibitors for HIV, and quetiapine.<sup>1</sup>

A potential weakness in our evaluation process is that most of the DDIs have never been studied, resulting in judgements based on 'expert opinion'. We have therefore assigned the lowest quality of evidence to these evaluations. These evaluations will be continually reviewed as data emerge and will be updated on [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org). The rapidly evolving nature of the COVID-19 field makes keeping the list of drugs up-to-date more challenging than our HIV, hepatitis and cancer websites. We run the ClinicalTrials.gov search regularly to identify new experimental COVID-19 therapies and survey our users as to which drugs they would find useful. We constantly review evidence, refine our interactions, and remove medications that are no longer in use. We propose to further develop the accessibility of the database by developing an app that will allow interactions to be viewed offline.

The risk of drug interactions should not necessarily preclude use of experimental therapies for COVID-19, since they are often manageable. For example, in critically ill patients, consideration should be given to stopping all but essential medications. Often there will be a need to balance the risk of 'theoretical' drug interactions against the benefit (often incompletely quantified) of new therapies. Safe management of drug interactions can only be carried out when prescribers are aware of their presence, underlining the importance of a full medicines reconciliation even for patients who present unwell and who are unable to give a detailed history. Our online resource is an attempt to increase recognition of harmful drug interactions and promote safe prescribing in critically unwell patients during the COVID-19 pandemic.

## Funding

This work was supported by the University of Liverpool Centre of Excellence in Infectious Disease Research, British HIV Association, European AIDS

Clinical Society, AbbVie, Gilead, Novartis, Merck Sharp & Dohme, and UKRI/NIHR. None of the funders had any input into any aspect of the writing of this manuscript.

## Transparency declarations

A.B. received grants and personal fees from Gilead and personal fees from AbbVie, outside the submitted work. C.M. received a research grant from Gilead and speaker honoraria from MSD and was also supported by the Adolf and Mary-Mil Foundation, outside the submitted work. D. Back received grants from AbbVie, Novartis, BHIVA, and EACS during the conduct of the study and grants from Merck, Gilead and ViiV outside the submitted work. F.M. received grants and personal fees from AbbVie and Gilead and personal fees from Janssen, MSD, and ViiV, outside the submitted work. S.K. has received research grants and speakers' honoraria from ViiV Healthcare, Gilead Sciences and AbbVie outside the submitted work. All other authors: none to declare.

## Author contributions

S.K., D. Back, F.M., C.M., A.B., and D. Burger conceived the study. C.H. and F.M. performed the literature review, F.M., C.M., A.B., S.K. and D. Back interpreted the data, S.G. and C.H. compiled figures, C.H. and S.K. wrote the manuscript, and all authors revised the manuscript.

## Supplementary data

Table S1 is available as [Supplementary data](#) at JAC Online.

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