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Potential Drug-Drug and Drug-Disease interactions of selected experimental therapies used in treating COVID-19 patients

Radhwan Nidal Al-Zidan

Department of Pharmaceutics, College of Pharmacy, University of Mosul, Iraq

ABSTRACT

At the end of 2019, the whole world was witnessing the birth of a new member of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) family in Wuhan city, China. Since then, the 2019 novel coronavirus (COVID-19) has rapidly invaded every corner of the world. Before the end of September 2020, nearly 32 million cases worldwide were recorded, with a death toll of approximately 1 million cases. As COVID-19 has spread across the world, certain groups of people prove more susceptible than others. Elderly patients and people with chronic medical conditions such as heart disease or diabetes are more likely to experience or even suffer from serious diseases. As a population, senior citizens take more medicines than young people. Similarly, people with chronic illnesses who are several taking drugs to control their illness. All this poses a significant query in managing COVID-19 cases: can a standard drug regimen be paired with one or more experimental drugs? For example, some of the most widely prescribed medicines—including antibacterial drugs, antifungals, heart-related medications, neuroleptics, contraceptives, and sedatives —can have extensive and often even severe interactions with some of the experimental COVID-19 therapy. Therefore, to reduce the morbidity and mortality rate associated with COVID-19, this issue needs to be answered in detail. This review addressed the key points related to the drug-drug and drug-disease interaction in patients with COVID-19. To help health care providers locate the answers they need in the shortest possible time, the information contained in this review has been included in easy-to-read tables.

Keywords: Drug interactions; DDIs; Polypharmacy; SARS-CoV-2; COVID-19.

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*Address for Correspondence:

Radhwan Nidal Al-Zidan (B.Sc. Pharm, M.Sc. Med. Biotech), Department of Pharmaceutics, College of Pharmacy, University of Mosul, Iraq

Introduction

Interactions between drugs could be described as the combination of two perhaps even more drugs, so that one drug's potency, sometimes even efficacy, is substantially altered by the existence of another medication. Adverse drug reactions (ADIs) well-documented causes of increasing patient morbidity as well as rising medical costs and complaints of malpractice.[1] Generally, drug interactions are known to include the effect(s) of one drug on the disposition and/or response to another. Normally such associations are addressed in pharmacokinetics-in which one medication alters the absorption, distribution, metabolism, or elimination (ADME) of another drug and pharmacodynamics-in which one medication affects the response to another medication (apart from the pharmacokinetic effects).[2] The effect of a patient's condition on the disposition and reaction to a medication is of equal significance.[3]Moreover, many medications adversely interfere with a variety of diseases, and vice versa. (i.e. drug-disease interactions). Unfortunately, this point has been scarcely addressed. Therefore, in addition to examining interactions between medications, this review also discusses interactions between the disease(s) and the experimental drugs used in COVID-19. An expanding number of studies have suggested that there is significant potential for ADIs occurrence in patients with COVID-19.[4] Moreover, since the start of COVID-19 pandemic numerous studies and clinical trials, continuously, suggest the use of an even increasing number of potential and adjuvant drugs.[5] Therefore, it is necessary to provide the healthcare providers with a comprehensive resource that contain all the possible drug-drug and drug-disease interaction in patients treated for COVID-19.

Currently, more than 200 thousand people are being infected with COVID-19 each day-worldwide.[6] This extremely high number of cases is a huge burden on the healthcare personnel; therefore, the healthcare professionals may not have the sufficient time to go through all the relevant articles

published about the safety of medications used in patients with COVID-19. That is why in this review all the information related to the drug-drug interactions as well as the drug-disease interactions was organized in easy-to-read comprehensive tables, as shown below in tables 1 & 2.

Table 1: Drug-Drug interactions of selected experimental therapies for COVID-19

Class of Drugs	Drug	Drug-Drug Interactions	Notes
Potential Antiviral Drugs	Azithromycin[7–11]	• Azithromycin stretches the QT interval, which raises the risk of developing cardiac arrhythmia and torsades de pointes. • Digoxin, diltiazem can prolong the PR interval and azithromycin has been shown to prolong the QT interval. • Azithromycin may potentiate the effects of oral anticoagulants.	Clinical monitoring, and likely serum digoxin levels, are recommended during and after azithromycin therapy is discontinued.
	Chloroquine[8,9,12–21]	• Chloroquine increases the hazard of prolonged QT interval in patients with COVID-19 who is also using Azithromycin. • Chloroquine enhances the pharmacodynamic action of the oral hypoglycemic drugs and Increases the risk of hypoglycemia. • Chloroquine is a moderate inhibitor of CYP2D6. Therefore, chloroquine could raise the serum concentrations of risperidone, metoprolol, aripiprazole, iloperidone, haloperidol, Tricyclic Antidepressants, fluoxetine, and paroxetine. On the contrary. Chloroquine will reduce the serum level of the prodrugs that are dependent on CYP2D6 for their activation. For instance, Tramadol and Codeine. • Chloroquine is an inhibitor of the transport system P-glycoprotein (P-gp). Therefore, Chloroquine is expected to rise the serum level of the cyclosporine.	
	Hydroxychloroquine (Plaquenil®)[7,13,15–18,21–25]	• Hydroxychloroquine decreases metabolism of beta-blockers such as carvedilol and metoprolol. • Hydroxychloroquine is an inhibitor of the transport system (P-gp). Therefore, increases the serum level of the substrates of this cellular pump inhibitor (such as cyclosporine and digoxin). • Hydroxychloroquine increases the risk of prolonged QT interval in patients with COVID-19 who is also using Azithromycin. • Hydroxychloroquine potentiates the effect of other medications that lengthen the QTc interval (e.x. Azithromycin & Domperidone). • Hydroxychloroquine enhances the pharmacodynamic action of the oral hypoglycemic drugs and Increases the risk of hypoglycemia. • Hydroxychloroquine is a moderate inhibitor of CYP2D6. Therefore, chloroquine could raise the serum concentrations of risperidone, metoprolol, aripiprazole, iloperidone, haloperidol, Tricyclic Antidepressants, fluoxetine, and paroxetine. On the contrary. Chloroquine will reduce the serum level of the prodrugs that are dependent on CYP2D6 for their activation. For instance, Tramadol and Codeine. • The risk of peripheral neuropathy may be increased if Hydroxychloroquine used concurrently with tocilizumab.	QT monitoring may be required.
	Favipiravir (Avigan®)[26,27]	• Coadministration of paracetamol and favipiravir increases paracetamol C_{max} and AUC. • Coadministration of theophylline and favipiravir increases favipiravir C_{max} and AUC.	In adults, the average dosage of paracetamol does not exceed 3 g/day (rather than 4 g/day).

	Lopinavir/Ritonavir (Kaletra®)[28–39]	Kaletra is a strong CYP2D6 and CYP3A4 inhibitor. Therefore, Kaletra decreases the pharmacological efficacy of prodrugs that requires enzymatic transformation in the liver to their active metabolite such as prasugrel and clopidogrel. On the contrary, drugs that are metabolized by CYP2D6 or CYP3A4 their serum levels are anticipated to rise dramatically. For instance, coadministration of Kaletra with sildenafil increases the sildenafil's AUC by 11-fold. • Kaletra inhibits the metabolism of Rivaroxaban (Xarelto®) and Ticagrelor (Brilinta®); therefore, increasing the risk of bleeding. • Kaletra accelerates the metabolism of Warfarin; therefore, Kaletra reduces the pharmacological action of Warfarin. • Kaletra increases the QT interval, thereby raising the risk of cardiac arrhythmia. Due to the obvious potential for severe adverse reactions such as arrhythmia, co-administration of Kaletra and amiodarone, lidocaine, bepridil or quinidine should be avoided. • Because of the high risk of severe adverse reactions such as rhabdomyolysis, co-administering simvastatin and Kaletra should be avoided.	There is a strong opportunity for multiple drug-drug interaction to occur as CYP2D6 and CYP3A4 are responsible for the vast majority of drug metabolisms. To prevent further complications, other antiviral medications like, Remdesivir or Favipiravir would be better alternatives for patients currently using prasugrel, clopidogrel or ticagrelor. ECG monitoring is recommended. If treatment with an HMG-CoA reductase inhibitor is suggested, the safest alternative would be to use pravastatin. Or you can use a lower dose of the statin drugs to avoid the serious side effects.
	Remdesivir (Veklury®)[40,41]	• • Remdesivir effect could be reduced by CYP3A4 inducers such as rifampicin, dexamethasone (at massive doses or with extended duration), phenytoin, carbamazepine, or phenobarbital. • Chloroquine or Hydroxychloroquine can diminish Remdesivir's antiviral activity. Therefore, it is not recommended to co-administer such medicines.	No clinical studies have been performed on drug-drug interactions for Remdesivir.
Immuno-modulators	Anakinra (Kineret®)[42,43]	• Enhances immunosuppression of other immunosuppressants. Therefore, it is not recommended to use it with TNF-blocking agents due to increased risk of infection	
	Convalescent plasma [44]	• No known interactions. However, it may inactivate live vaccines and diminish vaccine effectiveness.	Drugs should not be added to blood product IV infusion line.
	Dexamethasone[45-52]	• Dexamethasone enhances the immunosuppression of other immunosuppressants drugs. • On one hand, CYP3A4 inhibitors, (ex: cyclosporine, diltiazem, estrogens) increase the adverse effects/toxicity of Dexamethasone. On the other hand, CYP3A4 inducers (ex: phenobarbital, phenytoin, rifampicin) decrease the effect of Dexamethasone. • Dexamethasone may reduce the effect of Isoniazid, Aldesleukin, Caspofungin, Salicylates, Vaccines, &Inhibitors of Cholinesterase. • Dexamethasone may strengthen the effect and/or toxicity of Warfarin Cyclosporine, and Digoxin (by decreasing serum potassium).	In concurrent therapy with furosemide it is advisable to closely monitor the potassium levels as dexamethasone may cause hypokalemia, the effect of which will be enhanced by furosemide. Patients taking NSAIDs must be supervised because gastrointestinal ulceration can occur and/or become more severe.

	Tocilizumab (Actemra®)[53–60]	• May increase CYP450 enzyme activity. Therefore, it could decrease the serum levels of many medications thar are metabolized by the CYP450, such as Simvastatin. • The risk of peripheral neuropathy may be increased during concurrent use with hydroxychloroquine. • Coadministration of tocilizumab with immunosuppressive disease-modifying antirheumatic drug DMARDs (such as Leflunomide Or Methotrexate) or corticosteroids may lead to serious infections.	Concurrent therapy monitoring is required for the CYP450-metabolized drugs. Patients should be closely monitored for signs of neuropathy in the feet and hands, such as swelling, tingling, discomfort or numbness. Avoid concomitant use of DMARDs with tocilizumab.
	Ruxolitinib (Jakafi®)[58,60–65]	• Using rivaroxaban together with Ruxolitinib can increase the risk of bleeding, including severe and occasionally fatal hemorrhage. • When Ruxolitinib administered with strong CYP3A4 inhibitors such as Ketoconazole, Fluconazole, And Erythromycin dose modifications is required. • Coadministration of Ruxolitinib with immunosuppressive disease-modifying antirheumatic drug DMARDs (such as leflunomide or methotrexate) or immunosuppressive agents (high-dose corticosteroids, tofacitinib, basiliximab, and mycophenolic acid) may lead to serious infections along with lymphoma.	
	Sarilumab (Kevzara®)[31,41,66,67]	Using sarilumab together with adalimumab, baricitinib, etanercept, infliximab, may intensify the hazard of serious and potentially life-threatening infections. • Sarilumab may increase CYP450 enzyme activity. Therefore, it could decrease blood concentration & efficacy of many drugs thar are metabolized by the CYP450, such as Simvastatin, atorvastatin, amiodarone, diazepam, sildenafil, vardenafil, tadalafil, vinblastine, nifedipine, phenytoin, quinidine, alprazolam, theophylline, methylprednisolone, and dexamethasone.	Effects of Sarilumab on CYP450 can continue for weeks following its discontinuation.
Adjunctive Medications	Acetaminophen (Panadol®)[26,27,68,69]	• Coadministration of paracetamol and favipiravir increases paracetamol C_{max} and AUC. • Doses of Acetaminophen greater than 1.3 gm / day could enhance the anticoagulant activity of warfarin and increases the risk of bleeding.	The daily dose of paracetamol in adults should be no more than 3000 mg/day (rather than 4000 mg/day) when given with favipiravir. Patients with hepatic impairment may be at increased risk of toxicity. Close monitoring is mandatory in patients concurrently using medications well-known to induce hepatotoxicity such as Remdesivir.
	Bromhexine (Solvodin®)	• No clinically important unfavorable interactions have been reported with other medicines.	
	Famotidine (Pepcid ®) [70–73]	• Famotidine significantly increases the anticoagulant activity of warfarin and intensify the hazard of bleeding. • Famotidine reduces the hepatic metabolism of chloroquine, theophylline, phenytoin, propranolol, and lidocaine.	Adjustment of the warfarin dose may be necessary
	Vitamin C[74]	• Affects the excretion of drugs which are weak acids or bases can be diminished or increased, respectively. For instance, fluphenazine & Amphetamine are well-known examples for such interaction. • Vitamin C may reduce the anticoagulant activity of warfarin, and cyclosporine.	

	Vitamin D[75]	• Taking digoxin together with vitamin D can boost the effects of digoxin and lead to arrhythmia. • Taking large quantities of vitamin D along with diltiazem may reduce the efficacy of diltiazem.	
	Unfractionated Heparin (UFH) & Low Molecular Weight Heparins (LMWH)[76–79]	• UFH: increased risk of bleeding with other anticoagulants, antiplatelets, NSAIDs. • IV nitroglycerin may reduce heparin's anticoagulant effect. • LMWH: increased risk of bleeding with other anticoagulants, antiplatelets, NSAIDs.	
	Zinc[80,81]	• Zinc reduces the absorption of Quinolone &Tetracycline antibiotics (such as, Ciprofloxacin, Gatifloxacin, Moxifloxacin, Levofloxacin, Minocycline and Tetracycline). In addition, Zinc is implicated in hindering the absorption of other antibiotics-for instance, Cephalexin.	The doses used for COVID-19 in registered clinical trials differ among studies, with a maximum dose of 50 mg (elemental zinc) twice daily.

Table 2: Drug-Disease interactions of selected experimental therapies for COVID-19

Class of Drugs	Drug	Drug-Disease Interactions	Notes
Potential Antiviral Drugs	Azithromycin[56,82–88]	• Patients with noninfectious colitis or enteritis are at multiplied hazard of developing pseudomembranous colitis. • Azithromycin rises the hazard of prolonged cardiac repolarization and QT in patients with history of torsades de pointes, elongation of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval. • In general, the use of macrolide antibiotics has been reported to worsen symptoms of myasthenia gravis.	Stool test for C. difficile toxin and stool cultures for C. difficile could be beneficial diagnostically. It is suggested to use ECG to monitor patients during therapy. If signs and symptoms of hepatitis occur, Azithromycin should be stopped immediately.
	Chloroquine[89–97]	• Chloroquine use is commonly considered contraindicated in the presence of retinal or visual field changes. • The use of Chloroquine may exacerbate the medical condition in patients with porphyria. • Chloroquine rises the risk of elongated cardiac repolarization and QT in patients with history of torsades de pointes, elongated of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval. • Chloroquine may provoke epileptic seizures in prone individuals. Therefore, patients with low seizure threshold or epilepsy may be at greater risk. • Chloroquine may provoke acute renal failure and hemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency. • The use of Chloroquine may incite a severe attack of psoriasis.	Chloroquine should be ceased immediately if visual abnormalities (e.g., changes in visual acuity, loss of foveal reflex or pigmentary changes) develop. It is suggested to use ECG to monitor patients during therapy. Both of the hemoglobin and blood cell counts should be checked regularly.

	Hydroxychloroquine (Plaquenil®) [90–98]	• Hydroxychloroquine use is commonly considered contraindicated in the presence of retinal or visual field changes.. • The use of Hydroxychloroquine may exacerbate the medical condition in patients with porphyria. • Hydroxychloroquine rises the risk of elongated cardiac repolarization and QT in patients with history of torsades de pointes, elongated of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval. • Hydroxychloroquine may provoke epileptic seizures in prone individuals. Therefore, patients with low seizure threshold or epilepsy may be at greater risk. • Hydroxychloroquine may provoke acute renal failure and hemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency. • The use of Hydroxychloroquine may incite a severe attack of psoriasis.	Chloroquine should be ceased immediately if visual abnormalities (e.g., changes in visual acuity, loss of foveal reflex or pigmentary changes) develop. It is suggested to use ECG to monitor patients during therapy. Both of the hemoglobin and blood cell counts should be checked regularly.
	Favipiravir (Avifavir® [99,100]	• It is better to be avoided in patients with severely impaired renal or hepatic function	
	Lopinavir/Ritonavir (Kaletra®) [101–106]	• Lopinavir/Ritonavir is a known hepatotoxic. Therefore, Kaletra is better to be avoided in patients with hepatic impairment. • Patients with hemophilia are at an increased hazard of bleeding when given Lopinavir/Ritonavir. • Lopinavir/Ritonavir has been reported to elevate the blood glucose level. Therefore, it should be used with caution in patients with Diabetes Mellitus. • Second and third degree atrioventricular (AV) block have been reported with the use of Ritonavir. Therefore, in patients with pre-existing conduction irregularities, underlying heart disease, ischemic heart disease, or cardiomyopathies, Kaletra should be cautiously prescribed because such patients are at greater risk for developing cardiac conduction abnormalities.	
	Remdesivir (Veklury®) [107,108]	• The use of Remdesivir has been associated with Transaminase elevations in patients with COVID-19 and healthy volunteers. Therefore, Remdesivir should be used with caution in patients with hepatic impairment.	Hepatic laboratory testing is crucial at baseline and on daily basis during Remdesivir administration. Stop Remdesivir if the level of Alanine Aminotransferase (ALT) becomes more than 5 times the upper limit of normal (ULN).
Immuno-modulators	Anakinra (Kineret®) [109–111]	• Anakinra impedes the immune response. Therefore, Anakinra should not be given to patients with active infections or those who acquire severe infections after administration of Anakinra. • Anakinra is mainly excreted by the kidneys. Therefore, in patients with renal dysfunction it should be used with vigilance to prevent toxic reactions. • Anakinra should be used with vigilance in patients with hepatic diseases.	Patients with severe renal dysfunction or end-stage renal disease should receive the dose of Anakinra every other day. Monitoring of renal function is recommended.

	Dexamethasone (Decadron ®) [112-121]	• Dexamethasone might cause gastrointestinal hemorrhage and perforation. Therefore, Dexamethasone should be carefully administered or avoided in patients with ulcerative colitis, bowel anastomosis or diverticulitis. • Dexamethasone impedes the immune response. Therefore, Dexamethasone should not be commenced in actively infected patients or those who develop serious infections after its administration. • Dexamethasone can elevate blood glucose level by suppressing the secretion and antagonizing the action of insulin, which leads to augmented gluconeogenesis and suppression of peripheral glucose uptake. Therefore, Dexamethasone should be used with attentiveness in patients with Diabetes Mellitus. • Dexamethasone is mostly metabolized in the liver and may have higher pharmacological actions in patients with hepatic disease. • The use of dexamethasone in patients recently recovered from myocardial infarction can be related to left ventricular free-wall rupture. Hence, Dexamethasone should be used with extreme caution in myocardial infarction.	Dosage adjustments might be needed in patients with liver disease.
	Tocilizumab (Actemra®) [122,123]	• Tocilizumab impedes the immune response. Therefore, Tocilizumab should not be commenced in actively infected patients or those who develop serious infections after its administration. • Tocilizumab should be avoided or administered with great attentiveness in patients with hepatic impairment.	
	Ruxolitinib (Jakafi®) [124,125]	Ruxolitinib impedes the immune response. Therefore, it should not be started in patients with active infections or those who develop serious infections after Ruxolitinib administration.	Dose adjustment is required in patients with renal impairment.
	Sarilumab (Kevzara®) [66,126]	• Sarilumab may increase the risk of potentially life-threatening infections. Therefore, it should not be started in patients with active infections or those who develop serious infections after Sarilumab administration. • Sarilumab is associated with transaminase elevations. Therefore, Sarilumab is not advised for patients with hepatic impairment or active liver disease.	
Adjunctive Medications	Acetaminophen (Panadol® [127])	Acetaminophen must be used cautiously in patients with hepatic impairment.	
	Bromhexine (Solvodin®)	No clinically important unfavorable interactions have been reported with other medicines.	
	Famotidine (Pepcid ®) [72,128-130]	Famotidine should be used with caution in patients with impaired kidney function.	Adjustment of the dose is important in patients with renal impairment.
	Vitamin C [131]	• Vitamin C should be used vigilantly in patients with G 6 PD.	It is worth mentioning that high circulating concentrations of vitamin C can affect the accuracy of glucometers.

	Vitamin D [132–134]	• Vitamin D functions to increase the serum calcium concentration and can make arrhythmias worse, especially in patients taking digoxin. Therefore, high doses of vitamin D should be used cautiously in patients with arrhythmias. • In the presence of hyperphosphatemia, Vitamin D administration may lead to the precipitation of calcium-phosphate deposits within the renal or vascular systems.	Serum concentration of electrolytes should be corrected before initiating vitamin D therapy.
	Heparin & Low Molecular Weight Heparins (LMWH)[76–79,135–137]	Heparin & Low Molecular Weight Heparins (LMWH) significantly increases the risk of bleeding in patients suffering from hemophilia, severe liver disease, hypertensive or diabetic retinopathy, subacute bacterial endocarditis, or severe renal impairment.	
	Zinc [138–141]	• The trace metals, chromium and zinc, are excreted primarily in the urine. Supplemental doses of zinc may need to be reduced, or adjusted in patients with renal impairment. • Malabsorption syndromes reduce the amount of absorbed zinc. Therefore, larger dosages may be needed when zinc is given orally. • Long-term zinc intake may cause copper deficiency with associated reversible hematological defects (i.e., leukopenia, anemia) and possibly permanent neurological implications (i.e., paresthesia, myelopathy, spasticity, and ataxia).	

Discussion

Comorbid patients need several pharmacological treatments, which in turn may lead to issues that physicians are expected to handle rapidly by recognizing potential drug-drug interactions that could arise in order to prevent diminished efficacy or increased adverse event burden.[142] To put simply, the issue of whether concurrent pharmacological therapies that compromise patient safety is typically answered in a context that recognizes the treatment choices for each particular disease, enabling reasonable handling of interactions based on reliable clinical evidence.[143]However, in the case of comorbid conditions happening in COVID-19 patients, healthcare professionals now are needed to consider the hard question as to whether interactions between COVID-19 pharmacological treatments, which are not yet well-defined, and various therapeutic agents are possible.[144] Moreover, while waiting for the results from more than 300 ongoing clinical trials aimed at identifying successful treatments against the COVID-19 virus, how drugs used in COVID-19 patients (e.g., various Antiviral Agents, Azithromycin, Hydroxychloroquine, and Monoclonal Antibodies) that redundantly disturb the pharmacodynamics and pharmacokinetics of other drugs, and vice versa, remains a topic of investigation.[4,145]Therefore, focus is put on the interactions between the medications most widely used for COVID-19 and various classes of medications (Table 1) and the most important drug-disease interaction in (Table 2).

Given the range of potential interactions with hepatic metabolism systems, such as Cytochromes P450 (CYPs), as most of the existing antiviral medications used in COVID-19 infection are expected to affect various CYP450 isozymes. Therefore, dose adjustments may be needed. Some of the most challenging drug-drug interactions are between investigational COVID-19 medicines and cardiovascular medicines, including anti-arrhythmias, beta-blockers, calcium channel blockers, anti-coagulants, and lipid-lowering statins. Antibacterial medications are another significant class; many have a defined effect on the QT interval, and others may alter the level of a COVID-19 drug, a co-medication, or both in the body.[146,147] For instance, Rifampicin, can reduce the serum level of the experimental COVID-19 medication ritonavir/lopinavir by 75%. [148]

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