

Narrative Review of Anti-Retrovirals Used in COVID-19 Treatment

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Abstract. The COVID-19 pandemic has necessitated the exploration of various therapeutic strategies, including the repurposing of existing antiviral drugs. This narrative review examines the use of anti-retroviral agents in the treatment of COVID-19, focusing on their mechanisms of action, efficacy, and safety profiles. Key antiretrovirals discussed include Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, and Sofosbuvir. These agents primarily act by inhibiting RNA-dependent RNA polymerase (RdRp), a critical enzyme in the replication cycle of SARS-CoV-2. Clinical trials and in vitro studies have provided mixed results regarding their effectiveness, with some agents showing promise in reducing mortality and improving recovery times, while others have demonstrated limited efficacy. The review highlights the urgent need for further clinical research to optimize antiviral regimens and improve patient outcomes in the ongoing battle against COVID-19.

Keywords: COVID-19, anti-retroviral, SARS-CoV-2; RNA-dependent RNA polymerase; antiviral therapy.

Abstrak. Pandemi COVID-19 telah mendorong eksplorasi berbagai strategi terapeutik, termasuk penggunaan kembali obat antivirus yang sudah ada. Tinjauan naratif ini mengkaji penggunaan agen anti-retroviral dalam pengobatan COVID-19, dengan fokus pada mekanisme kerja, efektivitas, dan profil keamanannya. Beberapa anti-retroviral utama yang dibahas meliputi Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, dan Sofosbuvir. Agen-agen ini terutama bekerja dengan menghambat RNA-dependent RNA polymerase (RdRp), enzim krusial dalam siklus replikasi SARS-CoV-2. Uji klinis dan studi in vitro telah memberikan hasil yang beragam mengenai efektivitasnya, dengan beberapa agen menunjukkan potensi dalam mengurangi angka kematian dan mempercepat pemulihan, sementara yang lain menunjukkan efektivitas terbatas. Tinjauan ini menekankan perlunya penelitian klinis lebih lanjut untuk mengoptimalkan rejimen antiviral dan meningkatkan hasil pengobatan pasien dalam menghadapi COVID-19.

Kata kunci: COVID-19, anti-retroviral, SARS-CoV-2, RNA-dependent RNA polymerase, terapi antivirus.

1. INTRODUCTION

The COVID-19 pandemic, which emerged in 2019, remains a significant global health crisis. By the end of 2020, the World Health Organization had documented over 54 million confirmed cases worldwide, with more than 1.3 million fatalities (WHO, 2020). Indonesia has been notably affected, with a death toll of 16,945 out of 538,883 confirmed cases as of November 2020 (Kemenkes RI, 2020). In addition to preventive measures, enhancing therapeutic interventions is crucial to reduce the mortality rate among COVID-19 patients. Although vaccine development is ongoing, the immediate need posed by the pandemic has led to the repurposing of existing drugs as potential treatment options. Various therapeutic strategies have been implemented, particularly for patients in severe condition (Sadeghi et al., 2020; Setiadi et al., 2020).

Coronaviruses are large, enveloped, single-stranded RNA viruses capable of infecting a diverse range of species, including humans and various mammals like dogs, cats, cattle, and

pigs (Channappanavar et al., 2014; Wiersinga et al., 2020). These viruses are divided into four genera— α , β , γ , and δ —based on their genetic characteristics. The α and β coronaviruses primarily infect mammals (Rabi et al., 2020). SARS-CoV-2, which causes COVID-19, belongs to the Coronaviridae family (Wu & McGoogan, 2020). Human coronaviruses such as 229E and NL63, which lead to common respiratory illnesses like colds and croup, are classified within the α genus, whereas SARS-CoV, MERS-CoV, and SARS-CoV-2 are part of the β genus (Yuki et al., 2020).

The primary mode of SARS-CoV-2 transmission is through respiratory droplets from coughs or sneezes. Once inhaled, the virus targets type 2 alveolar epithelial cells (AT2) in the lungs, which are responsible for producing surfactant to reduce alveolar surface tension and prevent collapse. SARS-CoV-2 spike proteins have been found to bind with ACE-2 receptors on these cells (Li et al., 2019; Wang et al., 2020). ACE2 has been identified as the key receptor for SARS-CoV, with high expression levels observed in the lungs, heart, ileum, kidneys, and bladder (Zou et al., 2020). The roles of ACE2 and TMPRSS2, a cellular serine protease, are critical in facilitating the entry of SARS-CoV-2 into host cells, integrins may cause conformational changes in ACE2 when interacting with the virus (Hoffmann et al., 2020). Like other respiratory viruses such as influenza, SARS-CoV-2 can result in severe lymphopenia by targeting and destroying T lymphocytes. The virus-induced inflammatory response, involving both innate and adaptive immunity, hinders lymphopoiesis and increases lymphocyte apoptosis (Vaduganathan et al., 2020). As the infection progresses and viral replication accelerates, the integrity of the epithelial-endothelial barrier deteriorates. SARS-CoV-2 additionally targets pulmonary capillary endothelial cells, intensifying the inflammatory response and leading to the infiltration of monocytes and neutrophils. Autopsy reports have shown widespread thickening of alveolar walls, with mononuclear cells and macrophages invading air spaces, resulting in endotheliitis (Xu et al., 2020). Once inside the host cells, the virus releases its positive-sense single-stranded RNA (ssRNA), which hijacks the host's ribosomes to produce polyproteins and RNA-dependent RNA polymerase, both crucial for RNA replication. The spike proteins produced are distributed by cellular packaging structures to vesicular carriers, while cytoplasmic proteases break down the synthesized polyproteins into their components, such as nucleocapsid enzymes, spike protein, M-protein, and E-protein (Sigrist et al., 2020).

SARS-CoV-2 has the ability to induce the release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-10, tumor necrosis factor- α (TNF- α), monocyte chemoattractant protein 1 (MCP1), granulocyte-colony stimulating factor (G-CSF), and macrophage inflammatory protein (MIP) 1 α (Gong et al., 2020; Qin et al., 2020; Zhou et al., 2020). These

cytokines cause vasodilation and increase vascular capillary permeability, leading to plasma leakage into the alveolar interstitial space, which accumulates and exerts pressure on the alveoli (Wu et al., 2020). Elevated IL-6 levels have been associated with worse prognoses and greater clinical severity in COVID-19 patients (Ulhaq & Soraya, 2020). Moreover, COVID-19 patients have shown a greater proportion of specific inflammatory receptors, such as CD14 and CD16 monocytes, are observed, which contribute to IL-6 production and trigger a systemic inflammatory response. The overproduction and release of pro-inflammatory cytokines play a key role in the “cytokine storm,” which can overpower the immune system and result in acute respiratory distress syndrome (ARDS) and multi-organ dysfunction syndrome (MODS) (Nile et al., 2020).

The primary therapeutic strategy for COVID-19 focuses on symptomatic and supportive care. During the acute phase, immune-boosting drugs may be administered, while immunosuppressants can be considered in advanced or critical stages. Potential therapeutic options include chloroquine, hydroxychloroquine, antibiotics, tocilizumab, COVID-19 convalescent plasma, corticosteroids, vitamin B3, extracorporeal membrane oxygenation (EMCO), and antivirals. Nonetheless, no specific treatment has been conclusively demonstrated to be effective against COVID-19 (Sugitha, 2020). The choice of therapy should be individualized, weighing the benefits and risks of each drug. Numerous studies have been conducted to identify effective treatments, including the evaluation of antiviral effectiveness in COVID-19 therapy. This review will summarize the use of various antiviral drugs as potential therapeutic options for COVID-19.

2. METHODOLOGY

Scientific and clinical data related to the use of potential antiretroviral agents for the treatment of SARS-CoV-2 were collected through a comprehensive literature search. This search was conducted using the Google Scholar search engine with the keyword “SARS-CoV-2”.

3. RESULTS AND DISCUSSION

In this review, we compiled data on five antiretroviral agents that have been utilized in clinical settings to potentially treat SARS-CoV-2, aiming to reduce the mortality associated with COVID-19. The antiretrovirals examined include Remdesivir, Lopinavir/Ritonavir, Ribavirin, Oseltamivir, Favipiravir, and Sofosbuvir. These drugs primarily function as inhibitors of RNA-dependent RNA polymerase (RdRp), a key enzyme in the replication cycle

of RNA viruses. Focusing on RdRp has been a widely used approach in treating several viral infections, including hepatitis C virus (HCV), Zika virus (ZIKV), and human coronaviruses (HCoVs) (Elfiky, 2020). SARS-CoV-2, the virus responsible for COVID-19, shares about 79% of its genetic structure with SARS-CoV and approximately 50% with MERS-CoV (Gupta et al., 2020). The RdRp enzymes of SARS-CoV, SARS-CoV-2, and MERS-CoV are closely related (Wang et al., 2020), making RdRp a broad-spectrum target for identifying effective COVID-19 treatments. The antiretroviral agents listed in Table I are recognized by RdRp as substrates, thereby disrupting the replication of SARS-CoV-2 (Wang et al., 2020). In vitro studies have indicated that Remdesivir stands out as the most effective RdRp inhibitor, with an EC_{50} value of 0.77 μ M, which is significantly lower compared to Lopinavir/Ritonavir (EC_{50} = 26.1 μ M), Ribavirin (EC_{50} = 109.5 μ M), and Favipiravir (EC_{50} = 61.88 μ M).

Lopinavir/Ritonavir and Oseltamivir operate through different mechanisms. Lopinavir/Ritonavir acts as a protease inhibitor, while Oseltamivir inhibits neuraminidase via competitive inhibition. Protease inhibition has also been explored as a strategy for developing effective antiretroviral therapies against SARS-CoV-2. Proteases are enzymes that cleave proteins, a process essential for viral protein maturation. The primary protease responsible for cleaving polyproteins into functional proteins in SARS-CoV-2 is the 3 Chymotrypsin-like protease (3CL) (Li & Kang, 2020). Lopinavir/Ritonavir has demonstrated the ability to inhibit 3CL in vitro, with an EC_{50} value of 50 μ M and a K_i of 14 μ M (Wu et al., 2004). However, some studies have questioned the clinical effectiveness of Lopinavir/Ritonavir as a protease inhibitor, noting that in vitro EC_{50} data does not always translate into significant clinical improvements (Baden & Rubin, 2020; Cao et al., 2020; Horby et al., 2020). Oseltamivir, originally developed for treating influenza A and B, inhibits neuraminidase activity. Despite its early use during the COVID-19 outbreak, it was later discovered that SARS-CoV-2 does not express neuraminidase (Tan et al., 2020).

Sofosbuvir, which was previously used to treat SARS-CoV, has not been shown to inhibit SARS-CoV-2 according to bioinformatics studies (Jácome et al., 2020). Clinically, Sofosbuvir has been approved for treating hepatitis C virus (HCV) infection. Given the similarities in replication patterns between SARS-CoV-2 and HCV, there is a hypothesis that Sofosbuvir could be repurposed for treating SARS-CoV-2 (Sayad et al., 2020). To enhance clinical efficacy and prevent drug resistance, Sofosbuvir is currently administered in combination with other antiretroviral agents (Jockusch et al., 2020).

Table 1. Mechanism of Action, Dosage, Pharmacokinetic Profile, and Side Effects of Selected Antiretrovirals Potentially Used for COVID-19 Treatment

Antiviral Agent	Mechanism of Action	Dosage	Pharmacokinetic Profile and Side Effects
Remdesivir	Remdesivir, a nucleotide analog, is recognized by RNA-dependent RNA polymerase (RdRp) as a substrate. The complex formed between RDV and RdRp interferes with the termination process, effectively inhibiting the replication of MERS-CoV, SARS-CoV, and SARS-CoV-2, with an EC ₅₀ value of 0.77 μ M (Gordon et al., 2020; M. Wang et al., 2020).	Intravenous loading dose of 200 mg/24 hours, followed by a maintenance dose of 100 mg/24 hours for 5 to 9 days (Sun, 2020).	Metabolized by cytochrome P450 enzymes CYP2C8, CYP2D6, and CYP3A4. Elimination half-life ($t_{1/2}$) = 0.89 hours. AUC ₂₄ (Area Under Curve) over 24 hours of intravenous administration = 3,478.5 ng $\times$ h/ml, SEM = 923.5 ng $\times$ h/ml. Peak serum concentration (C _{max}) = 2,737 $\pm$ 1,985 ng/ml and 4,042 ng/ml (Gordon et al., 2020). Side effects: Elevated liver enzymes, constipation, nausea, respiratory failure (Fan et al., 2020).
Lopinavir/Ritonavir	Lopinavir functions as a competitive inhibitor of protease, and at a concentration of 50 μ M, it disrupts SARS-CoV chymotrypsin-like (3CL) protease, thereby interfering with proteolysis and leading to the formation of immature viral particles (Uzunova et al., 2020; Wu et al., 2004). It also hinders the replication of MERS-CoV and	The suggested dosage for treating SARS-CoV-2 is 200/50 mg to 400/100 mg administered every 12 hours for a duration of 7 to 10 days (Kim et al., 2020; Meini et al., 2020).	Lopinavir/Ritonavir is primarily metabolized by cytochrome P450 CYP3A4 (F. Li et al., 2012). Elimination half-life ($t_{1/2}$) = 4.0 hours. AUC ₁₂ after 10 days of oral administration = 102.9 $\pm$ 26.09 mg $\times$ h/L. Peak serum concentration (C _{max}) = 12.3 $\pm$ 3.22 mg/L (la Porte et al., 2004). Side effects: Diarrhea, nausea, vomiting, hyperlipidemia, glucose intolerance (Chandawi & Shuter, 2008).

	SARS-CoV, with an EC_{50} of 8.0 μM (Goldman et al., 2020). In Vero E6 cells infected with SARS-CoV-2, lopinavir shows an inhibitory effect on replication, with an EC_{50} of 26.1 μM (Choy et al., 2020). Ritonavir, when used in low doses, enhances the pharmacokinetics of lopinavir by inhibiting cytochrome P450 CYP3A4, thereby acting as a booster (Meini et al., 2020).		
Ribavirin	Prevents viral RNA synthesis and mRNA capping (Falzarano et al., 2013); attaches to SARS-CoV-2 RdRp, thereby hindering replication. In vitro studies on Vero E6 cells demonstrate an EC_{50} of 109.5 μM (Wang et al., 2020).	500 mg/12 hours intravenously (Tong et al., 2020); 600 mg/12 hours for 9 days (Eslami et al., 2020).	Elimination half-life ($t_{1/2}$) = 37.0 $\pm$ 14.2 hours. AUC₁₂ for oral administration = 37.2 mg$\times$h/L. Peak serum concentration (C_{max}) = 4,187 ng/ml and 638 ng/ml for intravenous and oral administration, respectively (G. F. Hoffmann & McKiernan, 2017; Rower et al., 2015). Side effects: Anemia, gastrointestinal disturbances, nausea, vomiting (Eslami et al., 2020).
Oseltamivir	Competitively inhibits neuraminidase, preventing viral release from cells and hindering virus crossing the respiratory mucosal layer (Hu et al., 2020).	300 mg/day (Tan et al., 2020).	Oseltamivir is a prodrug that is converted into its active form, oseltamivir carboxylate, through hydrolysis. Bioavailability is 75%, peak plasma concentration at 2.5-6 hours, protein binding: 3% (oseltamivir carboxylate), 42% (oseltamivir). Elimination half-life ($t_{1/2}$) = 1-3 hours (oseltamivir), 6-10 hours (oseltamivir

			carboxylate), excreted in feces; > 90% in urine as oseltamivir carboxylate (Chien et al., 2020). Side effects: Abdominal pain, conjunctivitis, ear disorders, epistaxis, insomnia, nausea, vomiting, vertigo (Tan et al., 2020).
Sofosbuvir	Suppresses the RNA-dependent RNA polymerase (RdRp) activity of SARS-CoV (Chien et al., 2020).	400 mg/day (Eslami et al., 2020).	Peak plasma concentration: 0.2-2 hours, protein binding: 61-65%, excreted in urine (78% as GS 331007 metabolite, 3.5% as sofosbuvir), $t_{1/2}$ = 0.4 hours (Eslami et al., 2020).
Favipiravir	Blocks RNA polymerase activity, with an EC_{50} of 61.88 μ M (Wang et al., 2020).	800-1800 mg/12 hours, maximum duration up to 14 days.	Bioavailability: 94%, protein binding: 54%, C_{max} at 2 hours after a single dose, t_{max} and $t_{1/2}$ increase with multiple doses, $t_{1/2}$ = 2.5-5 hours, rapidly eliminated by the kidneys in a hydroxylated form (Agrawal et al., 2020).

This review evaluated the effectiveness of various antiviral combinations for treating COVID-19. The regimen that included interferon beta-1b, Lopinavir/Ritonavir, and Ribavirin significantly shortened the time from the initiation of treatment to a negative nasopharyngeal swab result (7 days) compared to the control group (12 days). This treatment regimen also shortened both the duration of viral shedding and the length of hospital stay for patients with mild to moderate COVID-19. Side effects like nausea and diarrhea were generally mild and showed no significant differences between the two groups. It is noteworthy that one patient in the control group discontinued antiretroviral therapy due to hepatitis; however, no deaths were reported during the study (Hung et al., 2020).

The duration required for viral clearance varied across different antiviral combinations: Lopinavir/Ritonavir and IFN- α took 12 days, Ribavirin and IFN- α took 13 days, and Ribavirin with Lopinavir/Ritonavir took 15 days. The highest percentage of SARS-CoV-2 negative patients was observed in the Lopinavir/Ritonavir and IFN- α group (61.1%), followed by the Ribavirin and IFN- α group (51.5%), and the Ribavirin, Lopinavir/Ritonavir, and IFN- α group (46.9%) after 14 days of observation. However, these differences were not statistically

significant. Gastrointestinal side effects were more common in the Ribavirin, Lopinavir/Ritonavir, and IFN- α group compared to the other groups (Huang et al., 2020).

Sofosbuvir combined with Daclatasvir and Hydroxychloroquine reduced hospital stay duration in COVID-19 patients (6 days) compared to Hydroxychloroquine combined with Lopinavir/Ritonavir (8 days). The intervention group was administered Sofosbuvir and Daclatasvir (400/60 mg once daily) with or without Lopinavir/Ritonavir (200/50 mg twice daily), whereas the control group was given only Lopinavir/Ritonavir (200/50 mg twice daily). Additionally, both groups were treated with Hydroxychloroquine (200 mg twice daily) (Sadeghi et al., 2020).

The combination of Sofosbuvir, Daclatasvir, and Ribavirin did not reduce the length of hospital stay; however, the cumulative recovery rate was higher, with fewer patients requiring ICU admission compared to the control group. The intervention group was treated with Sofosbuvir and Daclatasvir (400/60 mg once daily) in combination with Ribavirin (600 mg twice daily), whereas the control group was administered Hydroxychloroquine (400 mg as a single dose) and Lopinavir/Ritonavir (400/100 mg twice daily) with or without Ribavirin (600 mg twice daily). A limitation of this study was the small sample size and the higher median age in the control group compared to the intervention group (Kasgari et al., 2020).

In a study comparing Remdesivir to a placebo, no significant difference was found in clinical improvement; however, patients treated with Remdesivir showed faster clinical recovery (less than 10 days). Adverse effects were reported in 66% of the intervention group and 64% of the placebo group (Wang et al., 2020). There was no statistically significant difference in clinical status between patients treated with Remdesivir for 10 days and those who received standard care. However, those who received a 5-day course of Remdesivir showed statistically significant clinical improvement compared to the standard care group. The average treatment duration was 5 days for the 5-day Remdesivir group and 6 days for the 10-day group. By day 11, patients in the 5-day Remdesivir group experienced statistically significant clinical improvement compared to those in the standard care group, whereas no significant difference was observed between the 10-day Remdesivir group and the standard care group. By day 28, nine patients had died: two (1%) from the 5-day Remdesivir group, three (2%) from the 10-day Remdesivir group, and four (2%) from the standard care group. Side effects, including nausea, hypokalemia, and headaches, were more commonly reported in patients treated with Remdesivir than in those receiving standard care (Spinner et al., 2020).

Tabel 2. Mechanism of Action, Dosage, Pharmacokinetic Profile, and Side Effects of Selected Antiretrovirals Potentially Used for COVID-19 Treatment

Trial ID and Reference	Location	Design	Number of Patients	Intervention	Control	Inclusion Criteria	Primary Outcome
NCT04276688 (Hung et al., 2020)	Hong Kong, China	Open-label randomized controlled trial	127	The combination treatment included Lopinavir/ritonavir at 400 mg/100 mg taken twice daily, Ribavirin at 400 mg taken twice daily for 14 days, and Interferon Beta-1B administered subcutaneously at 0.25 mg for 3 days (n=86).	Lopinavir/ritonavir 400 mg/100 mg twice daily (n=41)	- Adults aged 18 years or older - Body temperature of 38°C or higher accompanied by symptoms such as cough, sputum production, sore throat, nasal discharge, myalgia, headache, or fatigue - Symptoms present for 10 days or less	The duration until a negative SARS-CoV-2 result is obtained in nasopharyngeal swab samples.
IRCT20200324046850 N2 (Eslami et al., 2020)	Tehran, Iran	Open-label trial	62	Combination of Sofosbuvir/Daclatasvir 400/60 mg	Ribavirin 600 mg every 12 hours	- Positive RT-PCR nasopharyngeal swab result - O₂ saturation <94%	Time from treatment initiation to hospital discharge

ChiCTR2000029387 (Huang et al., 2020)	China	Open-label randomized controlled trial	101	Combination of Ribavirin 2 g intravenously (loading dose) followed by 400-600 mg every 8 hours + IFN- α 50 mg twice daily (n=33)	Combination of Lopinavir/ritonavir + IFN- α 50 mg twice daily (n=36); Combination of Lopinavir/ritonavir + IFN- α 50 mg twice daily + Ribavirin 2 g intravenously (loading dose) followed by 400-600 mg every 8 hours (n=32)	1. Aged 18-65 years 2. Confirmed diagnosis of mild to moderate COVID-19	Time from antiviral treatment initiation to negative SARS-CoV-2
IRCT20200328046886 N1 (Abbaspour Kasgari et al., 2020)	Mazandaran, Iran	Randomized clinical trial	48	Combination of Sofosbuvir/Daclatasvir 400/60 mg + Ribavirin 600 mg twice daily	Hydroxychloroquine (400 mg as a single dose) and Lopinavir/ritonavir (400/100 mg taken twice daily), with or without Ribavirin (600 mg administered twice daily).	1. Aged 18-80 years 2. Confirmed diagnosis of mild to moderate COVID-19 3. Respiratory rate <24/min 4. O₂ saturation <94%	Length of hospital stay
NCT04257656 (Wang et al., 2020)	Wuhan, China	Randomized, double-blind, placebo-controlled,	237	Remdesivir was administered intravenously at a dose of 200 mg on the first	Placebo administered with the same volume (n=79)	1. Not pregnant 2. Aged $\geq$18 years 3. Pneumonia present	Clinical improvement after 28 days

		multicenter trial		day, followed by a daily infusion of 100 mg from day 2 to day 10 (n=158).		4. O₂ saturation <94% 5. PaO₂ <300 mmHg	
NCT04292730 (Spinner et al., 2020)	USA, Europe, Asia	Randomized controlled trial	596	Remdesivir was given intravenously at a dose of 200 mg on the first day, followed by 100 mg on the following days as part of 5-day and 10-day regimens (n=396).	Standard care (n=200)	1. Positive COVID-19 pneumonia 2. O₂ saturation >94%	Distribution of clinical status using a 7-point ordinal scale on day 11 of the study.
ChiCTR2000030254 (Chen et al., 2020)	Wuhan, China	Open-label, prospective, randomized (multicenter)	236	Favipiravir administered at 1600 mg twice daily on day 1, followed by 600 mg twice daily from days 2 to 10, in addition to standard care (n=116).	Arbidol (Umifenovir) at 200 mg taken three times daily, in addition to standard care (n=120).	1. Positive COVID-19 pneumonia 2. Symptom onset within 12 days	Clinical improvement rate at 7 days
ChiCTR2000029600 (Cai et al., 2020)	Shenzhen, China	Open-label, non-randomized	80	Favipiravir at a dosage of 1600 mg twice daily on the first day, followed by 600 mg twice daily from days 2 to 14, combined with inhaled	Lopinavir at 400 mg combined with Ritonavir at 100 mg, both administered twice daily, along with inhaled aerosol	1. Positive COVID-19 by swab 2. Aged 16-75 years 3. Symptom onset ≤7 days	Viral clearance

				aerosol IFN- α 5 iu administere d twice daily (n=35).	IFN- α at 5 iu twice daily (n=45).		
IRCT20200 128046294 N2 (Sadeghi et al., 2020)	Tehran, Iran	Open- label randomi zed (multice nter)	66	Sofosbuvir and Daclatasvir at 400/60 mg taken once daily, combined with Hydroxych loroquine at 200 mg twice daily, with or without Lopinavir/ Ritonavir at 200/50 mg twice daily (n=33).	Lopinavir/ Ritonavir at 200/50 mg administer ed twice daily, combined with Hydroxyc hloroquin e at 200 mg twice daily (n=33).	1. Positive COVID-19 by swab/chest CT Hospitalized 2. Oral temperature $\geq 37.8^{\circ}\text{C}$, O_2 saturation $< 94\%$, RR $> 24/\text{min}$ 3. Symptom onset ≤ 8 days	Recover y within 14 days

The comparison between Favipiravir and Arbidol showed no significant difference in clinical improvement on day 7, although mild and manageable side effects were associated with Favipiravir use. The intervention group received Favipiravir (1600 mg twice daily on the first day, followed by 600 mg twice daily from day 2 to day 10), while the control group received Arbidol (200 mg three times daily) alongside standard therapy (which included traditional Chinese medicine, additional antivirals, antibiotics, immunomodulators, psychotropics, nutritional supplements, cardiovascular drugs, and invasive/non-invasive ventilation) for 7 days (Chen et al., 2020).

Favipiravir showed superior results in terms of disease progression and viral clearance when compared to the control group. The intervention group was administered Favipiravir (1600 mg twice daily on the first day, followed by 600 mg twice daily from day 2 to day 14), while the control group was given Lopinavir/Ritonavir (400 mg/100 mg twice daily). Additionally, both groups received aerosolized IFN- α inhalation therapy (5 iu twice daily) (Cai et al., 2020).

4. CONCLUSION

The use of anti-retroviral agents in the treatment of COVID-19 has been explored with varying degrees of success. This review highlights that while some agents such as Remdesivir have shown promise in reducing viral load and improving clinical outcomes, others, like Lopinavir/Ritonavir, have demonstrated limited efficacy. The inhibition of RNA-dependent RNA polymerase (RdRp) remains a crucial mechanism for targeting SARS-CoV-2. However, the mixed results across clinical trials underline the necessity for continued research to optimize antiviral regimens and improve therapeutic outcomes for COVID-19 patients. Future studies should focus on large-scale clinical trials to establish the most effective combinations of these agents, tailored to different stages of the disease and patient conditions.

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REFERENCES

- Abbaspour Kasgari, H., Moradi, S., Shabani, A. M., Babamahmoodi, F., Davoudi Badabi, A. R., Davoudi, L., Alikhani, A., Hedayatzadeh Omran, A., Saeedi, M., Merat, S., Wentzel, H., Garratt, A., Levi, J., Simmons, B., Hill, A., & Tirgar Fakheri, H. (2020). Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: A single-centre, randomized controlled trial. *Journal of Antimicrobial Chemotherapy*, 75 (11), 3373–3378. <https://doi.org/10.1093/jac/dkaa332>
- Agrawal, U., Raju, R., & Udwadia, Z. F. (2020). Favipiravir: A new and emerging antiviral option in COVID-19. *Medical Journal Armed Forces India*, 76 (4), 370–376. <https://doi.org/10.1016/j.mjafi.2020.08.004>
- Anand, K., Karade, S., Sen, S., & Gupta, R. (2020). SARS-CoV-2: Camazotz's Curse. *Medical Journal Armed Forces India*, 76 (2), 136-141.
- Baden, L. R., & Rubin, E. J. (2020). Covid-19 — The search for effective therapy. *New England Journal of Medicine*, 382 (19), 1851–1852. <https://doi.org/10.1056/NEJMe2005477>
- Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., ... Liu, L. (2020). Experimental treatment with favipiravir for COVID-19: An open-label control

- study. *Engineering*, 6 (10), 1192–1198. <https://doi.org/10.1016/j.eng.2020.03.007>
- Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., ... Wang, C. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*, 382 (19), 1787–1799. <https://doi.org/10.1056/NEJMoa2001282>
- Chandawi, A., & Shuter, J. (2008). Lopinavir/ritonavir in the treatment of HIV-1 infection: A review. *Therapeutics and Clinical Risk Management*, 4 (5), 1023–1033.
- Channappanavar, R., Zhao, J., & Perlman, S. (2014). T cell-mediated immune response to respiratory coronaviruses. *Immunologic Research*, 59n(1–3), 118–128. <https://doi.org/10.1007/s12026-014-8534-z>
- Chen, C., Zhang, Y., Huang, J., Yin, P., Cheng, Z., Wu, J., Chen, S., Zhang, Y., Chen, B., Lu, M., Luo, Y., Ju, L., Zhang, J., & Wang, X. (2020). Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. *medRxiv*. <https://doi.org/10.1101/2020.03.17.20037432>
- Chien, M., Anderson, T. K., Jockusch, S., Tao, C., Li, X., Kumar, S., Russo, J. J., Kirchdoerfer, R. N., & Ju, J. (2020). Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *Journal of Proteome Research*, 19 (11), 4690–4697. <https://doi.org/10.1021/acs.jproteome.0c00392>
- Choy, K.-T., Wong, A. Y.-L., Kaewpreedee, P., Sia, S. F., Chen, D., Hui, K. P. Y., Chu, D. K. W., Chan, M. C. W., Cheung, P. P.-H., Huang, X., Peiris, M., & Yen, H.-L. (2020). Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Research*, 178, 104786. <https://doi.org/10.1016/j.antiviral.2020.104786>
- Elfiky, A. A. (2020). Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sciences*, 248,*117477. <https://doi.org/10.1016/j.lfs.2020.117477>
- Elfiky, A. A. (2020). SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: An in silico perspective. *Journal of Biomolecular Structure and Dynamics*, 1–9. <https://doi.org/10.1080/07391102.2020.1761882>
- Eslami, G., Mousaviasl, S., Radmanesh, E., Jelvay, S., Bitaraf, S., Simmons, B., Wentzel, H., Hill, A., Sadeghi, A., Freeman, J., Salmanzadeh, S., Esmaeilian, H., Mobarak, M., Tabibi, R., Jafari Kashi, A. H., Lotfi, Z., Talebzadeh, S. M., Wickramatillake, A., Momtazan, M., ... Mobarak, S. (2020). The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *Journal of Antimicrobial Chemotherapy*, 75 (11), 3366–3372. <https://doi.org/10.1093/jac/dkaa331>
- Falzarano, D., de Wit, E., Martellaro, C., Callison, J., Munster, V. J., & Feldmann, H. (2013). Inhibition of novel β coronavirus replication by a combination of interferon- α 2b and ribavirin. *Scientific Reports*, 3, 1686. <https://doi.org/10.1038/srep01686>
- Fan, Q., Zhang, B., Ma, J., & Zhang, S. (2020). Safety profile of the antiviral drug remdesivir: An update. *Biomedicine & Pharmacotherapy*, 130, 110532.

<https://doi.org/10.1016/j.biopha.2020.110532>

- Glass, C. A., Cash, J. C., & Mullen, J. (2020). Coronavirus disease (COVID-19). In *Family Practice Guidelines*. Springer Publishing Company. <https://doi.org/10.1891/9780826153425.0016b>
- Goldman, J. D., Lye, D. C. B., Hui, D. S., Marks, K. M., Bruno, R., Montejano, R., Spinner, C. D., Galli, M., Ahn, M.-Y., Nahass, R. G., Chen, Y.-S., SenGupta, D., Hyland, R. H., Osinusi, A. O., Cao, H., Blair, C., Wei, X., Gaggar, A., Brainard, D. M., & Subramanian, A. (2020). Remdesivir for 5 or 10 days in patients with severe COVID-19. *New England Journal of Medicine*, 383 (19), 1827–1837. <https://doi.org/10.1056/NEJMoa2015301>
- Gong, J., Dong, H., Xia, S. Q., Huang, Y. Z., Wang, D., Zhao, Y., Liu, W., Tu, S., Zhang, M., Wang, Q., & Lu, F. (2020). Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv*. <https://doi.org/10.1101/2020.02.25.20025643>
- Gordon, C. J., Tchesnokov, E. P., Woolner, E., Perry, J. K., Feng, J. Y., Porter, D. P., & Götte, M. (2020). Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *Journal of Biological Chemistry*, 295 (20), 6785–6797. <https://doi.org/10.1074/jbc.RA120.013679>
- Hoffmann, G. F., & McKiernan, P. (2017). The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. In *Inherited Metabolic Diseases: A Clinical Approach* (pp. 203–226). https://doi.org/10.1007/978-3-662-49410-3_24
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 181 (2), 271-280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Horby, P. W., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Emberson, J., Palfreeman, A., Raw, J., Elmahi, E., Prudon, B., Green, C., Carley, S., Chadwick, D., Davies, M., Wise, M. P., Baillie, J. K., Chappell, L. C., Faust, S. N., Jaki, T., & Landray, M. J. (2020). Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (Recovery): A randomised, controlled, open-label, platform trial. *The Lancet*, 396 (10259), 1345–1352. [https://doi.org/10.1016/S0140-6736\(20\)32013-4](https://doi.org/10.1016/S0140-6736(20)32013-4)
- Hu, F., Yin, G., Chen, Y., Song, J., Ye, M., Liu, J., Chen, C., Song, Y., Tang, X., & Zhang, Y. (2020). Corticosteroid, oseltamivir and delayed admission are independent risk factors for prolonged viral shedding in patients with coronavirus disease 2019. *The Clinical Respiratory Journal*, 14 (11), 1067–1075. <https://doi.org/10.1111/crj.13243>
- Huang, Y. Q., Tang, S. Q., Xu, X. L., Zeng, Y. M., He, X. Q., Li, Y., Harypursat, V., Lu, Y. Q., Wan, Y., Zhang, L., Sun, Q. Z., Sun, N. N., Wang, G. X., Yang, Z. P., & Chen, Y. K. (2020). No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus infection (COVID-19). *Frontiers in Pharmacology*.

<https://doi.org/10.3389/fphar.2020.01071>

- Hung, I. F. N., Lung, K. C., Tso, E. Y. K., Liu, R., Chung, T. W. H., Chu, M. Y., Ng, Y. Y., Lo, J., Chan, J., Tam, A. R., Shum, H. P., Chan, V., Wu, A. K. L., Sin, K. M., Leung, W. S., Law, W. L., Lung, D. C., Sin, S., Yeung, P., & Yuen, K. Y. (2020). Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomised, phase 2 trial. *The Lancet*. *[https://doi.org/10.1016/S0140-6736\(20\)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4)
- Jácome, R., Campillo-Balderas, J. A., Ponce de León, S., Becerra, A., & Lazcano, A. (2020). Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. *Scientific Reports*, 10 (1), 9294. <https://doi.org/10.1038/s41598-020-66440-9>
- Jockusch, S., Tao, C., Li, X., Chien, M., Kumar, S., Morozova, I., Kalachikov, S., Russo, J. J., & Ju, J. (2020). Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by remdesivir. *Scientific Reports*, 10 (1), 16577. <https://doi.org/10.1038/s41598-020-73641-9>
- Kementerian Kesehatan Republik Indonesia. (2020). *Situasi COVID-19*. <https://www.kemkes.go.id>
- Kim, S. B., Huh, K., Heo, J. Y., Joo, E.-J., Kim, Y. J., Choi, W. S., Kim, Y.-J., Seo, Y. Bin, Yoon, Y. K., Ku, N. S., Jeong, S. J., Kim, S.-H., Peck, K. R., & Yeom, J. S. (2020). Interim guidelines on antiviral therapy for COVID-19. *Infection & Chemotherapy*, 52 (2), 281. <https://doi.org/10.3947/ic.2020.52.2.281>
- la Porte, C. J. L., Colbers, E. P. H., Bertz, R., Voncken, D. S., Wikstrom, K., Boeree, M. J., Koopmans, P. P., Hekster, Y. A., & Burger, D. M. (2004). Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrobial Agents and Chemotherapy*, 48 (5), 1553–1560. <https://doi.org/10.1128/AAC.48.5.1553-1560.2004>
- Li, F., Lu, J., & Ma, X. (2012). CYP3A4-mediated lopinavir bioactivation and its inhibition by ritonavir. *Drug Metabolism and Disposition*, 40(1), 18–24. <https://doi.org/10.1124/dmd.111.041400>
- Li, Q., & Kang, C. B. (2020). Progress in developing inhibitors of SARS-CoV-2 3C-like protease. *Microorganisms*, 8 (8), 1250. <https://doi.org/10.3390/microorganisms8081250>
- Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K., Greenough, T. C., Choe, H., & Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426 (6965), 450–454. <https://doi.org/10.1038/nature02145>
- Li, Z., Tomlinson, A. C., Wong, A. H., Zhou, D., Desforges, M., Talbot, P. J., Benlekbir, S., Rubinstein, J. L., & Rini, J. M. (2019). The human coronavirus HCoV-229E S-protein structure and receptor binding. *eLife*, 8, e51230. <https://doi.org/10.7554/eLife.51230>
- Meini, S., Pagotto, A., Longo, B., Vendramin, I., Pecori, D., & Tascini, C. (2020). Role of lopinavir/ritonavir in the treatment of Covid-19: A review of current evidence, guideline recommendations, and perspectives. *Journal of Clinical Medicine*, 9 (7), 2050. <https://doi.org/10.3390/jcm9072050>

- Nile, S. H., Nile, A., Qiu, J., Li, L., Jia, X., & Kai, G. (2020). COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine & Growth Factor Reviews*, 53, 66–70. <https://doi.org/10.1016/j.cytogfr.2020.05.002>
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., & Tian, D.-S. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical Infectious Diseases*, 71 (15), 762–768. <https://doi.org/10.1093/cid/ciaa248>
- Rabi, F. A., Al Zoubi, M. S., Kasasbeh, G. A., Salameh, D. M., & Al-Nasser, A. D. (2020). SARS-CoV-2 and coronavirus disease 2019: What we know so far. *Pathogens*, 9 (3), 231. <https://doi.org/10.3390/pathogens9030231>
- Rower, J. E., Meissner, E. G., Jimmerson, L. C., Osinusi, A., Sims, Z., Petersen, T., Bushman, L. R., Wolfe, P., McHutchison, J. G., Kottlil, S., & Kiser, J. J. (2015). Serum and cellular ribavirin pharmacokinetic and concentration–effect analysis in HCV patients receiving sofosbuvir plus ribavirin. *Journal of Antimicrobial Chemotherapy*, 70 (8), 2322–2329. <https://doi.org/10.1093/jac/dkv122>
- Sadeghi, A., Ali Asgari, A., Norouzi, A., Kheiri, Z., Anushirvani, A., Montazeri, M., Hosamirudisai, H., Afhami, S., Akbarpour, E., Aliannejad, R., Radmard, A. R., Davarpanah, A. H., Levi, J., Wentzel, H., Qavi, A., Garratt, A., Simmons, B., Hill, A., & Merat, S. (2020). Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): A randomized controlled trial. *Journal of Antimicrobial Chemotherapy*, 75 (11), 3379–3385. <https://doi.org/10.1093/jac/dkaa334>
- Sayad, B., Sobhani, M., & Khodarahmi, R. (2020). Sofosbuvir as repurposed antiviral drug against COVID-19: Why were we convinced to evaluate the drug in a registered/approved clinical trial? *Archives of Medical Research*, 51 (6), 577–581. <https://doi.org/10.1016/j.arcmed.2020.04.018>
- Setiadi, A. P., Wibowo, Y. I., Halim, S. V., Brata, C., Presley, B., & Setiawan, E. (2020). Tata laksana terapi pasien dengan COVID-19: Sebuah kajian naratif. *Indonesian Journal of Clinical Pharmacy*, 9 (1), 70. <https://doi.org/10.15416/ijcp.2020.9.1.70>
- Sigrist, C. J., Bridge, A., & Le Mercier, P. (2020). A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral Research*, 177, 104759. <https://doi.org/10.1016/j.antiviral.2020.104759>
- Spinner, C. D., Gottlieb, R. L., Criner, G. J., Arribas López, J. R., Cattelan, A. M., Soriano Viladomiu, A., Ogbuagu, O., Malhotra, P., Mullane, K. M., Castagna, A., Chai, L. Y. A., Roestenber, M., Tsang, O. T. Y., Bernasconi, E., Le Turnier, P., Chang, S. C., Sengupta, D., Hyland, R. H., Osinusi, A. O., & Marty, F. M. (2020). Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical trial. *JAMA*, 324 (11), 1048–1057. <https://doi.org/10.1001/jama.2020.16349>
- Sugitha, K. S. L. (2020). COVID-19: Respon imunologis, ketahanan pada permukaan benda dan pilihan terapi klinis. *Intisari Sains Medis*, 11 (2), 791–797. <https://doi.org/10.15562/ism.v11i2.746>

- Sun, D. (2020). Remdesivir for treatment of COVID-19: Combination of pulmonary and IV administration may offer additional benefit. **AAPS Journal*, 22 (4), 77. <https://doi.org/10.1208/s12248-020-00459-8>
- Tan, Q., Duan, L., Ma, Y., Wu, F., Huang, Q., Mao, K., Xiao, W., Xia, H., Zhang, S., Zhou, E., Ma, P., Song, S., Li, Y., Zhao, Z., Sun, Y., Li, Z., Geng, W., Yin, Z., & Jin, Y. (2020). Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study. *Bioorganic Chemistry*, 104, 104257. <https://doi.org/10.1016/j.bioorg.2020.104257>
- Tong, S., Su, Y., Yu, Y., Wu, C., Chen, J., Wang, S., & Jiang, J. (2020). Ribavirin therapy for severe COVID-19: A retrospective cohort study. *International Journal of Antimicrobial Agents*, 56 (3), 106114. <https://doi.org/10.1016/j.ijantimicag.2020.106114>
- Ulhaq, Z. S., & Soraya, G. V. (2020). Interleukin-6 as a potential biomarker of COVID-19 progression. *Médecine et Maladies Infectieuses*, 50 (4), 382–383. <https://doi.org/10.1016/j.medmal.2020.04.002>
- Uzunova, K., Filipova, E., Pavlova, V., & Vekov, T. (2020). Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2. *Biomedicine & Pharmacotherapy*, 131, 110668. <https://doi.org/10.1016/j.biopha.2020.110668>
- Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J. V., Pfeffer, M. A., & Solomon, S. D. (2020). Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *New England Journal of Medicine*, 382 (17), 1653–1659. <https://doi.org/10.1056/NEJMSr2005760>
- Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, 30 (3), 269–271. <https://doi.org/10.1038/s41422-020-0282-0>
- Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., Lu, G., Qiao, C., Hu, Y., Yuen, K.-Y., Wang, Q., Zhou, H., Yan, J., & Qi, J. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*, 181 (4), 894-904.e9. <https://doi.org/10.1016/j.cell.2020.03.045>
- Wang, Y., Anirudhan, V., Du, R., Cui, Q., & Rong, L. (2020). Recent updates in the pharmacological management of COVID-19. *Letters in Applied NanoBioScience*, 10 (1), 1969-1980.
- Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., ... Wang, C. (2020). Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*, 395(10236), 1569–1578. [https://doi.org/10.1016/S0140-6736\(20\)31022-9](https://doi.org/10.1016/S0140-6736(20)31022-9)
- Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *JAMA*, 324 (8), 782. <https://doi.org/10.1001/jama.2020.12839>

- World Health Organization. (2020). *Coronavirus disease (COVID-19) pandemic*. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- Wu, C. Y., Jan, J. T., Ma, S. H., Kuo, C. J., Juan, H. F., Cheng, Y. S. E., Hsu, H. H., Huang, H. C., Wu, D., Brik, A., Liang, F. S., Liu, R. S., Fang, J. M., Chen, S. T., Liang, P. H., & Wong, C. H. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences of the United States of America*. <https://doi.org/10.1073/pnas.0403596101>
- Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., ... Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine*, 180 (7), 934. <https://doi.org/10.1001/jamainternmed.2020.0994>
- Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA*, 323 (13), 1239. <https://doi.org/10.1001/jama.2020.2648>
- Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F.-S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*, 8 (4), 420–422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
- Yuki, K., Fujiogi, M., & Koutsogiannaki, S. (2020). COVID-19 pathophysiology: A review. *Clinical Immunology*, 215, 108427. <https://doi.org/10.1016/j.clim.2020.108427>
- Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., Sun, R., Tian, Z., Xu, X., & Wei, H. (2020). Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *National Science Review*, 7 (6), 998–1002. <https://doi.org/10.1093/nsr/nwaa041>
- Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine*, 14 (2), 185–192. <https://doi.org/10.1007/s11684-020-0754-0>