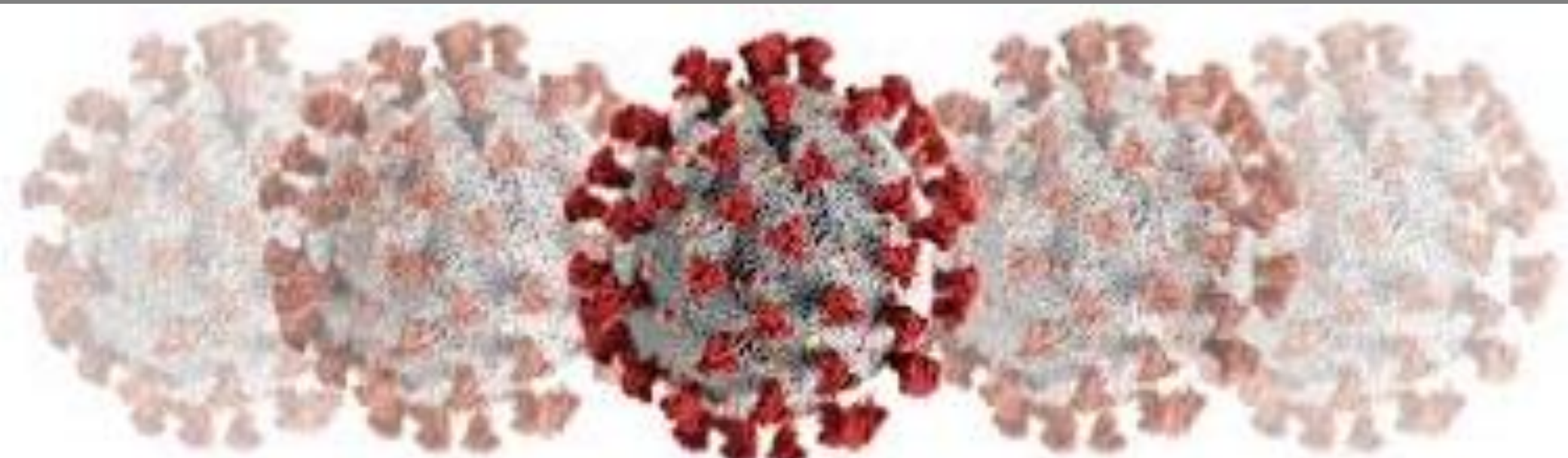
TONY BLAIR INSTITUTE FOR GLOBAL CHANGE

COVID-19: Guidance for Governments Assessing Treatments

March 2020



Executive summary

1. What drugs are or will be available to treat Covid-19?

- Therapeutic treatments for Covid-19 should be considered after (1) prevention measures that reduce disease transmission; and (2) supportive care measures (such as ventilators and medical oxygen) that manage the symptoms of Covid-19.
- While there is currently no treatment for Covid-19, nor any robust clinical evidence that supports a particular treatment, many clinical trials are underway to assess potential treatments. WHO has launched the Solidarity Trial to assess the four most promising treatments.
- Treatments, if approved, are unlikely to be life-saving, but more likely to have an impact on the early stage of the disease.
- Governments should also develop a vaccine strategy to access vaccine supplies when one is proven.

2. What can governments do to procure treatments once they are approved and available?

- Work with other governments and multilateral institutions to develop a global pact to ensure the availability of stock is not hoarded by first-comers.
- Engage market aggregators and funders (e.g. CHAI and the Global Fund) to procure treatments and benefit from their buying power, financing, existing supply chains and demand-forecasting capabilities.
- Build relationships with pharmaceutical companies and manufacturers that own the IP for treatments to secure stocks.

3. What should governments consider in the administration of treatments?

- Ramp up the skills of health-care professionals to administer supportive care and treatments quickly.
- Deciding who to treat is complicated. Issue clear guidance in the administration of treatments (and patient-care prioritisation) and create government systems that support and enforce this.
- Collect real-time data via electronic health records, which on aggregate can provide actionable insights to clinicians.

4. What should governments be communicating to citizens about Covid-19 treatments?

- Clearly communicate that currently no treatments are clinically proven to treat Covid-19. Set expectations that treatments and a vaccine are coming but the process takes time.
- Establish the facts about treatments and bust myths to protect citizens from the risks of self-medication, over-dosing and the use of alternative remedies.
- Reassure existing patients with other conditions that their treatment will continue as normal in spite of any drug repurposing.

There is currently no established treatment for Covid-19

Immediate/Short-Term Options

Medium-Term/Stemming-Recurrence Options

In the absence of established treatment, current clinical management entails **infection prevention** and **control measures** and **supportive care** such as supplementary oxygen.

Drug Repurposing

Hundreds of small-scale clinical trials are underway to establish efficacy of drugs marketed for treatment of other conditions in promoting viral clearance of Covid-19. But, there is currently **no robust evidence nor consensus in the scientific community to support the usage of these drugs as treatments for Covid-19**. Should this be demonstrated, these drugs offer certain advantages:

- Already available, domestically or for import, with possibility manufacturers could increase production.
- Generic versions of majority of most-promising drugs available.
- Existing evidence on safety and drug tolerance in humans.
- Potential for expedited regulatory approval processes of drugs found to be effective.

Compound Scanning

Pharmaceutical manufacturers scanning libraries of antiviral compounds and assessing likely viability for Covid-19 treatment. Scarce public information available. **All in pre-clinical exploratory phase** so will require approval for clinical testing, a four-phase trial for safety and efficacy and regulatory approval for use.

Antibodies

Either harvested from recovered patients or bioengineered. Patient-to-patient transfers possible in line with standard protocols but not all antibodies are functional and availability depends on proportion of infected patients who recover and donate cells. Optimal **storage conditions are unique to each antibody** and can be easily damaged.

Vaccines

Experimental development being undertaken globally but overwhelmingly in pre-clinical stage with only one in Phase I for human safety testing. Development, trial and approval – prior to manufacture and distribution – **may take up to 18 months so unlikely to be available for use in the current pandemic**.

The WHO has launched a global trial of the most promising treatments to use off-label for Covid-19 across 45 countries[1]

	Treatment description[2]	Classification	Ongoing & completed # Covid-19 trials	Biological plausibility[3]	Suitability for use in Africa[3]	Patent holder / generic Y/N	Cost of drug in Africa[4]	Time to market[4]	Region/s licensed
1	**Remdesivir** Developed to combat the DRC Ebola outbreak. Studies show the drug inhibits coronaviruses that cause SARS and MERS.	Anti-viral (novel)	5 / 0			GILEAD No	$$$	6-12 months	Not licensed
2	**Hydroxychloroquine** Used for the treatment of malaria, lupus and rheumatoid arthritis.	Anti-malarial	20+ / 0			Patent Expired Yes	$$	0-6 months	
3	**Chloroquine** Used for the treatment of malaria, lupus and rheumatoid arthritis.	Anti-malarial	20+ / 0			Patent Expired Yes	$	0-6 months	
4	**Lopinavir/ Ritonavir (Kaletra)** Combination drug, used to treat HIV infections.	Anti-viral combination	3+ / 1			abbvie[5] Yes	$	0-6 months	
5	**Lopinavir/Ritonavir + Interferon-Beta** Experimental treatment that combines Interferon Beta a drug used to treat Multiple Sclerosis patients with Lopinavir/Ritonavir.	Anti-viral / immuno-modulator combination	3+ / 0			abbvie Yes	$$$	0-9 months	

Key: Globally approved. On WHO Essential Medicines list — Globally approved.

Source: 1. Science (22.03.2020); WHO media briefing (27.03.2020); WHO database of publications of COVID-19. 2. See Annex for greater detail. 3. Based on TBI's interviews with expert medical professionals. 4. Indicative costs and times. The MSF Access Campaign provides data on the cost of treatments. 5. Abbvie has given up its patent rights to Kaletra in response to COVID-19.

How to assess the suitability of treatments for Covid-19

Criteria

- Drugs already approved/marketed for other conditions (especially broad-spectrum anti-virals with likely efficacy on respiratory conditions/ RNA viruses)
- Evidence from clinical trials conducted in-country or region
- Significant number of active/proposed trials for Covid-19 repurposing
- Applicability within the national health-care systems e.g. ease of storage and administration
- Safety/low adverse effects

Considerations for policymakers

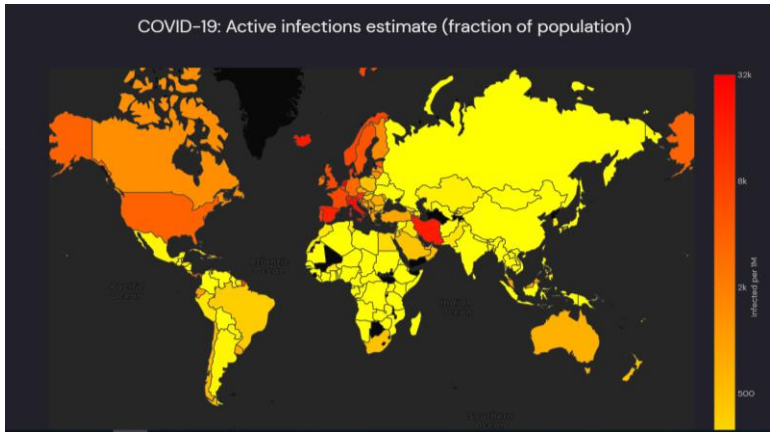
- Governments must make decisions based on scientific evidence.
- Medical advisors should monitor the most promising clinical trials and research and governments should participate in these. Clinical trials should be complemented with widespread testing.
- Host populations have different characteristics and treatments may not be transferable.
- Ensure that the use of unproven drugs does not create a shortage of those medicines to treat diseases for which they have proved effective (chloroquine for malaria; lopinavir/ritonavir for HIV).

"We call on countries to refrain from therapeutics that have not been demonstrated to be effective in the treatment of Covid-19. The history of medicine is strewn with examples of drugs that worked on paper, or in a test tube, but didn't work in humans or were actually harmful. We must follow the evidence. There are no shortcuts."[1] (WHO Director General)

Sources: 1. WHO Director-General's opening remarks at the media briefing on COVID-19 (27.03.2020); Oxford Centre for Evidence-Based Medicine

Use open-source research and data to generate demand forecasts for your country

Institutions providing data, modelling & research



- Africa-focused communities of experts
- CDC Africa
- Cochrane
- Imperial College London
- International Severe Acute Respiratory & Emerging Infection Consortium
- Future of Humanity Institute, University of Oxford
- John Hopkins University
- Liverpool School of Tropical Medicine
- London School of Hygiene & Tropical Medicine
- National Institute of Health Research (UK)
- Oracle
- Robert Koch Institut (Germany)
- Wellcome Trust
- World Bank
- World Health Organisation

Considerations for policymakers

- Modelling is required to assess countries' demand for equipment and treatments.
- Build relationships with the global scientific community to benefit from the latest research and data to input into models and forecasts.
- International research institutions have resources available to help countries develop models for their own population characteristics that are unique.
- Make your national data available to the scientific community to contribute to models and forecasts for the epidemiology of Covid-19 in Africa.
- Connect decision-makers to data scientists to enable them to make decisions based on the latest evidence.
- Ring-fence research staff to support trials.
- Oracle's Therapeutic Learning System has launched in the US and can capture, aggregate and analyse real-time data on treatment, working as a complement, not substitute for clinical trials.

Sources: List of organisations committed to sharing their data and research openly (Wellcome Trust, 2020)

Plan financing for medicines now

Most significant medicines financiers

TheGlobalFund	Largest grant funding mechanism in global health. Sub-contracts market aggregators to procure and distribute medicines and health products to low- and medium-income countries. Issued guidance that governments can repurpose 5% of all GFATM resources for Covid-19 response.
Bill & Melinda Gates foundation	Committed $100m for the global response to the 2019 novel coronavirus, including to develop vaccines, treatments and diagnostics. Funding to multi-lateral organisations like WHO and the African Field Epidemiology Network and the Covid-19 Therapeutics Accelerator.
USAID	USAID and the State Department have pledged $274m to help countries respond. USAID's Health Bureau has existing programmes on Emerging Pandemic Threats and invests in medical commodities.
AFREXIMBANK	A $3 billion Pandemic Trade Impact Mitigation Facility (PATIMFA), to help African countries deal with the economic and health impacts, including emergency trade finance for import of urgent needs including medicine, medical equipment, hospital refitting etc.
AFRICA PHILANTHROPY NETWORK	International philanthropy networks facilitate donations from HNWIs in diaspora. The African Philanthropy Network: one of several mobilising donations from HNWI on the continent.

Considerations for policymakers

- In the current international environment, bilateral relationships will prove more responsive and effective in accessing financing than multilateralism.
- Leverage existing sectoral relationships between ministries of health and donor agencies.
- Repurpose existing donor grants and programmes to address the crisis.
- Leverage partnerships to help identify and address critical supply challenges, jointly manage demand and accelerate the regulatory approval pathway.
- Launch diaspora appeals to fill financing gaps.

Sources: Global Fund, USAID, Gates Foundation, African Philanthropy Network, Afrexim Bank, African Field Epidemiology Network

Supply-chain considerations for policymakers

Procure

Use established organisations with pooled procurement capabilities to maximise value for money and efficiency.

Engage WHO for guidance on quality assurance, especially when purchasing generic alternatives.

Build direct relationships with pharmaceutical companies trialling drugs.

Manufacture

Identify if active pharmaceutical ingredients (APIs) can be sourced regionally. Engage reputable local/ regional manufacturers of drugs where possible to lock-in commodities and shorten the supply chain.

Organisations such as the MSF Access Campaign provide quality assurance and monitoring across the supply chain.

Ship

Air and sea lines face disruption because of quarantine periods and reduced travel. North-South and South-South lanes currently less affected but capacity and prices may change at short notice.

Prepare the regulatory environment to expedite imports clearance and distribution.

Clear & store

Engage regulatory authorities to define emergency mechanisms for approval and clearance of medicines while maintaining safety. Provide clear guidance on expanded access and compassionate use to physicians.

Protect stock. Secure drug-storage facilities, consider prescription and price controls for relevant drugs, and ensure adherence to prescription procedures.

Distribute

Make preparations for “last mile” delivery (e.g. temperature control versus cold-chain).

Use all available supply chains including faith-based hospitals and local manufacturers.

Consider how restrictions on movement might hamper in-country distribution and make appropriate exemptions.

Organisations with pooled procurement capability are best placed to help broker and manage treatment supply

Supply-chain organisations offer advantages, including full-service solutions

- Outsourced negotiations with pooled demand across clients to get the best prices through economies of scale.
- Access to network of quality-assured manufacturers worldwide.
- Access to network of local logistics agents for warehousing and in-country distribution.
- Support in obtaining product registration in-country.

Considerations for policymakers

- Pooled procurement is only as good as your national demand-forecasting capability and supply chain.
- Mass procurement organisations provide political leverage. Governments should work with them and other governments to develop a global pact to ensure the equitable availability of stock.

CLINTON HEALTH ACCESS INITIATIVE

Programmes in 18 African countries and access agreement markets across the continent, sourcing drugs from manufacturers globally.

UNDP

Supports implementation of Global Fund Grants, expertise in health care in crisis and post-crisis environments.

IDA FOUNDATION

Generic pharmaceuticals sourced in Europe and Asia, supplied exclusively in Africa, with focus on Chinese and Indian manufacturers.

unicef

Supply Division offers knowledge, purchasing capacity and logistics expertise to procure health-care commodities.

MISSIONPHARMA

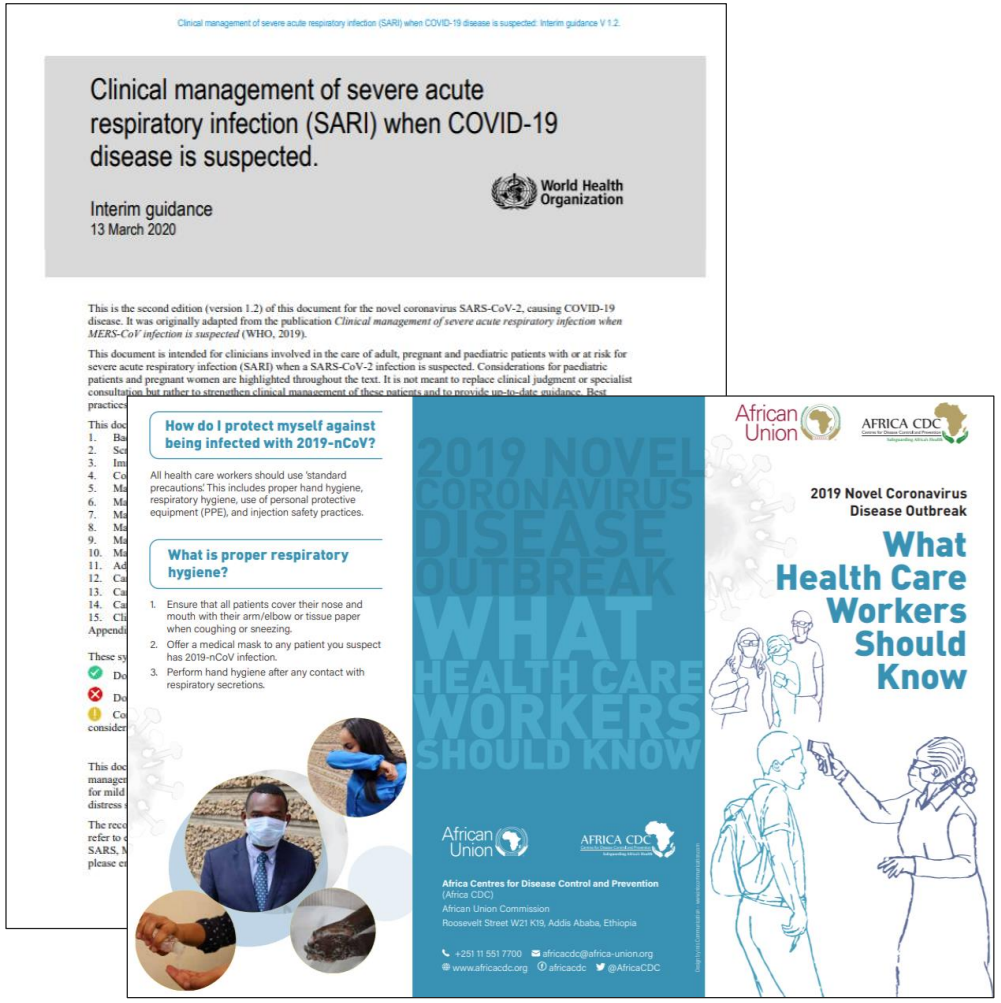
Complete supply-chain management for government and private customers in 130 countries.

Unitaid

Supports the Medicines Patent Pool to share medicines IP and broker procurement. Has financing capability through levies on the aviation industry.

Sources: Clinton Health Access Initiative, IDA Foundation, Missionpharma, UNDP, UNICEF, WHO, Unitaid

Once drugs are distributed, weigh up a range of treatment-administration considerations



Considerations for policymakers

- Ramp up the expertise of health-care professionals to administer supportive care and treatments quickly.
- Issue clear guidance in the administration of treatments and create government systems that support and enforce this.
- Use and share care guidelines from/with other national health systems.
- Depending on stocks and expert consensus, consider the administration of unproven treatments on compassionate grounds. In general, medics should preserve treatments for their intended use and government may limit the use of unproven treatments to the framework of a clinical trial.
- Deciding who to treat is complicated. Issue guidance to health-care professionals on ethical patient-care prioritisation aligned with procedures for the equitable distribution of treatments[1].

Sources: 1. WHO's INTEGRATE framework provides criteria for decision-making in public health

Proactively communicate treatment decisions to the public and explain how care will be prioritised

	Risk	Mitigation
Establish the facts	Public misunderstands the viability and availability of different treatment options and mounts political pressure for hasty action	• Do not allow questions about treatment to dominate your narrative. Hype around individual treatments can be counter-productive, leading to hoarding, self-medication and over-dosing. • Emphasise the importance of preventing transmission and supportive care. • Investigate fake news re. treatments and penalise proponents. Use public messaging to myth-bust. Avoid overstating/making decisive statements about a drug's safety or effectiveness. Do not draw on anecdotal evidence. Be clear that trials are experimental and guidance from experts will determine if, when and which drugs will be used off-label.
Address the question of equity	Trust in government declines if it is not transparent how patients are prioritised for treatment or if the poor and marginalised are not provided for	• Reassure patients with other conditions that their treatment will continue as normal in spite of any drug repurposing and work with mass procurement organisations to guarantee this. • Engage with WHO regional offices to better understand emerging practice in applying the INTEGRATE criteria to the Covid-19 outbreak in the ethical prioritisation of care provision, and how this can be contextualised for your country's profile. • Assure the public (potentially through trusted third parties) that decisions will be informed by evidence, clinical judgement and a clear framework. • Use a range of communication methods to ensure poor, vulnerable and isolated people can obtain information, for example those who cannot read or do not have access to technology.
Discourage self-medication	Black markets emerge to enable unprescribed access to drugs and natural extracts that are still undergoing clinical trials due to media coverage	• Warn the public about opportunists and scams: prices may be high and there is no way to verify what drugs they are being sold. • Be clear about toxicity risks of self-medication, especially where a case is not confirmed. Indicate the system is likely to already be under pressure without these additional patients. • Be clear that most people with the virus will have only mild symptoms and not require any treatment. Reiterate how self-medication may deny others drugs they actually need.
Emphasise science-based interventions	Public evade containment measures and shun medical treatment in favour of traditional healing	• Recognise the sensitivities around traditional healing in your cultural context. • Be clear how contact with traditional healers is likely to further spread the virus. • Counterbalance narratives that reference a lack of established treatment. Be clear how rapidly the global scientific community has mobilised. Indicate the relationships the government has. • Target your messaging for groups who are most likely to depend on traditional healing or do not ordinarily have access to medicine. Indicate how you will help them to access treatment.

Annex

Remdesivir

Drug Classification	Developer/Patent Holder	Countries of Use
Anti-viral	Gilead Sciences (United States)	United States (investigational)
Administration Route	**Licensed Manufacturers**	
Intravenous	None	

Approved Use	Other Experimental Uses
None	• Used during Ebola outbreak in the DRC and found to be less effective than alternative treatments.

Findings/Limitations - Small Scale Clinical Trials	Status - Ongoing Larger Scale Trials
• Limited preclinical data on MERS and SARS indicate that drug may have potential activity against COVID-19. • The first COVID-19 patient diagnosed in the United States was given the drug when his condition worsened and improved the next day. • A Californian patient who received the drug and whom doctors thought might not survive also recovered.	• On 20 February, China was reported to have initiated two clinical trials to determine the safety and efficacy of the drug. Reported that trials will be complete by April and the drug licensed as early as May. • On 20 February, the US National Institute of Allergy and Infectious Diseases (NIAID) commenced a randomized, controlled multi-center clinical trial run by the University of Nebraska Medical Center (UNMC) in up to 50 sites globally and involving 394 participants to evaluate the safety and efficacy of the drug. Completion expected by April 23. • On 15 March, Gilead initiated two Phase 3 randomized, open-label clinical studies to evaluate its safety and efficacy. Also included in clinical trial of four treatments as part of WHO Solidarity, during which more than 3,000 patients will be treated.

Availability	Cost	Political Narrative
Gilead has temporarily stopped new emergency access outside of clinical trials due to surge in demand. Likely 6-12 months to ramp up production to meet global demand.	Gilead is expected to price the drug at around $900 to $1,000 or lower per course.	Nothing of note to date

Sources: Gilead, Science, Time, Kaiser Health News, Bloomberg, Nature, National Institutes of Health, US National Library of Medicine, New England Journal of Medicine, Inserm, Biopharmadive, RBC Capital Markets

Chloroquine and hydroxychloroquine

Drug Classification	Developer/Patent Holder	Countries of Use
Anti-malarial	Expired	Worldwide (for approved uses) China, South Korea, France, Senegal, United States (for Covid-19, investigational or emergency authorisation). WHO Essential Medicine
Administration Route	**Licensed Manufacturers**	
Oral	Various, notably Novartis, Mylan, Teva, Bayer.	

Approved Use	Other Experimental Uses
• Approved by US Food and Drug Administration for treatment of malaria, lupus and rheumatoid arthritis. • On 29 March 2020 the FDA issued an emergency use authorisation, approving the use of both drugs to treat patients infected by coronavirus, despite no large clinical trials having taken place.	• None
Findings/Limitations - Small Scale Clinical Trials	
• Doctors in China, South Korea, France, Senegal and the United States are now giving the drug to some patients with Covid-19 with promising, albeit anecdotal results so far. • Controversial and small study in France showed that hydroxychloroquine appeared to help clear the virus from 26 out of 40 patients. • Over 20 clinical trials have been registered concerning use.	• The Covid Therapeutics Accelerator ($125m in seed funding from Bill and Melinda Gates Foundation, Mastercard Foundation and Wellcome Trust) will randomize 40,000 participants in Europe & Asia over 1 year. • Food and Drug Administration, National Institutes of Health and the Biomedical Advanced Research and Development Authority planning US trials. • Included in WHO Solidarity clinical trials.

Availability	Cost	Political Narrative
Widely available. Manufacturers are issuing donations. Novartis pledged 130 million hydroxychloroquine tablets worldwide. Teva donating 16 million tablets to US hospitals.	60 tablets (one months' worth) cost around £6.	• On March 21, President Trump described the drug as a "game-changer". The FDA has encouraged caution. • The UK and India have announced export bans of the drugs.

SOURCE: Nature, Nature, Live Science, Chinese Clinical Trial Register , FiercePharma, University of Oxford; Covid-19 Therapeuctics Accelerator

Lopinavir/Ritonavir (Kaletra)

Drug Classification	Developer/Patent Holder	Countries of Use
Combination of two antiretrovirals	AbbVie (United States)*	Worldwide (for approved uses) WHO Essential Medicine
Administration Route	**Licensed Manufacturers**	
Oral (liquid, capsule, tablet)	AbbVie announced intention not to enforce patents, allowing for wider manufacturing and distribution.	

Approved Use	Other Experimental Uses
• Approved by the US Food and Drug Administration for the treatment of HIV.	• Experimental use for SARS and MERS patients, though with ambiguous results.
Findings/Limitations - Small Scale Clinical Trials	**Status - Ongoing Larger Scale Trials**
• First trial involved 199 patients in Wuhan, China. Explored use of lopinavir/ritonavir combination for patients critically ill will COVID-19. Reported no significant difference between treatment and control group. Possibility that drugs may be effective for patients with less severe case.	• Included in clinical trial of four possible treatments as part of WHO Solidarity. • At least 2 others announced/recruiting clinical trials. Oxford University launched a clinical RECOVERY trial on March 22. The 'Reacting Consortium' led by Lyon University also launched separate trial, 'Discovery'.

Availability	Cost	Political Narrative
Widely available	Recommended monthly dose for HIV of approx. 60 tablets costs around $42 in Africa. Price may decrease since the patent has been forfeited.	• The UK has announced a parallel export ban of Kaletra. • *AbbVie has given up its patent rights in response to COVID-19.

SOURCE: Science, Nature, Financial Times, New England Medical Journal, Clinical Trials Arena, AbbVie, International Medical Products Price Guide, Medicine Patent Pool Clinical Trials.gov Registered Trials

Lopinavir/Ritonavir + Interferon-Beta

Drug Classification	Developer/Patent Holder	Countries of Use
Lopinavir/ritonavir is combination of two antiretroviral, interferon-beta is immunomodulator	AbbVie (United States)*	Worldwide (for approved uses)
Administration Route	**Licensed Manufacturers**	
Injection	Various, notably Biogen and Pfizer	

Approved Use	Other Experimental Uses
• Lopinavir/ritonavir approved by the US Food and Drug Administration for the treatment of HIV. • Interferon-beta approved by US Food and Drug Administration for management of relapsing forms of Multiple Sclerosis.	• Treatment of marmosets infected with MERS.
Findings/Limitations - Small Scale Clinical Trials	**Status - Ongoing Larger Scale Trials**
• No reported findings as yet. • However, it has been suggested that the use of interferon-beta on patients with severe COVID-19 might be risky. If it is given late in the disease it could worsen tissue damage. • It is an example of a specialty drug that would require a refrigerated chain of distribution.	• Included in clinical trial of four possible treatments as part of WHO Solidarity. • There are currently at least 2 other ongoing clinical trials which have been announced which will be studying the effects of Lopinavir/Ritonavir on Covid-19 patients. 1.The 'Reacting Consortium' led by Lyon University launched a separate trial called 'Discovery'. 2. The Hospital Authority of Hong Kong – Study Start date February 10th 2020, estimated primary completion date January 31st, 2020.

Availability	Cost	Political Narrative
Widely available.	Unknown	• *AbbVie has given up its patent rights to Lopinavir/Ritonavir in response to COVID-19.

SOURCE: Science, Nature, Financial Times Clinical Trials.gov, ScienceDirect, Clinical Trials Arena Registered Trials

Favipiravir (Avigan)

Drug Classification	Developer/Patent Holder	Countries of Use
Anti-viral	Toyama Chemical (Japan)	Japan (since 2014) China (since February 2020) Italy (experimentally, since March 2020)
Administration Route	**Licensed Manufacturers**	
Oral	Hisun Pharmaceutical (China)	

Approved Use	Other Experimental Uses
Influenza strains that are resistant to other treatment.	Preliminary findings for efficacy against Ebola, supplied by Japan to Guinea for this purpose.

Findings/Limitations - Small Scale Clinical Trials	Status - Ongoing Larger Scale Trials
• At least six preliminary clinical trials completed in China. Participants for others currently being recruited, though none have thus far been double-blind, placebo-controlled. Suggest faster viral clearance/recovery from symptoms and higher improvement rate in chest imaging with favipiravir treatment relative to control treatments including lopinavir, ritonavir and umifenovir but limitations include small sample sizes/lack of data on long-term safety and efficacy. • On 18 March, the National Center for Biotechnology Development in China officially recommended the drug to medical teams and suggested its inclusion in the country's treatment plan.	

Availability	Cost	Political Narrative
Japanese government has 2m stockpile. Developer has assembled response team. On 30 March, Toyama Chemical announced it will increase production.	Unknown	• Japanese Prime Minister Shinzo Abe expressed support for using favipiravir for treatment and announced intention to expedite approval. • Philippines has requested an allocation.

Sources: Proceedings of the Japan Academy, Disaster Medicine and Public Health Preparedness, Engineering, Drug Discoveries and Therapeutics, Drug Bank, Financial Times, Council on Foreign Relations, The Mainichi, The Times, Il Fato Quotidiano