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PERSPECTIVE

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The time to offer treatments for COVID-19

Binh T. Ngo[a,b], Paul Marik[a], Pierre Kory[c], Leland Shapiro[d], Raphael Thomadsen[e], Jose Iglesias[f], Stephen Ditmore[g], Marc Rendell[b], Joseph Varon[h], Michael Dubé[a], Neha Nanda[a], Gino In[a], Daniel Arkfeld[a], Preet Chaudhary[a], Vito M. Campese[a], Diana L. Hanna[a], David E. Sawcer[a], Glenn Ehresmann[a], David Peng[a], Miroslaw Smogorewski[a], April Armstrong[a], Rajkumar Dasgupta[a], Fred Sattler[a], Denise Brennan-Rieder[i], Cristina Mussini[j], Oriol Mitja[k], Vicente Soriano[l], Nicolas Peschanski[m], Gilles Hayem[n], Marco Confalonieri[o], Maria Carmela Piccirillo[p], Antonio Lobo-Ferreira[q], Iraldo Bello Rivero[r], Mika Turkia[s], Eivind H. Vingevoll[t], Daniel Griffin[d,u#] and Ivan Fn Hung [ID][d#]

[a]Department of Internal Medicine, Eastern Virginia Medical School, Pulmonary and Critical Care Medicine, Norfolk, USA; [b]The Rose Salter Medical Research Foundation, Newport Coast, USA; [c]Pulmonary and Critical Care Medicine, Aurora St. Luke's Medical Center, Milwaukee, USA; [d]Department of Internal Medicine, Rocky Mountain Regional Veterans Affairs Medical Center in Aurora, CO and University of Colorado Anschutz Medical Campus in Aurora, CO Supported by the Emily Foundation, Boston, USA; [e]Department of Marketing, Washington University, St. Louis, USA; [f]Department of Internal Medicine, Jersey Shore University Medical Center, Hackensack Meridian School of Medicine at Seton Hall, Neptune, USA; [g]Health Reporting, Parkchester Times, USA; [h]United Memorial Medical Center, University of Texas School of Medicine, Houston, USA; [i]CoronaTracker Community Research Group, Canada; [j]Department of Infectious Disease, University of Modena and Reggio Emilia, Modena, Italy; [k]Department of Internal Medicine, Hospital Universitari Germans Trias I Pujol, Badalona, Spain; [l]Director, Centro Medico, UNIR Health Sciences School & Medical Center, Madrid, Spain; [m]Department of Emergency Medicine, UniversityHospital of Rennes, Rennes, France; [n]Department of Rheumatology, Hôpital Paris Saint-Joseph, Paris, France; [o]Department of Respiratory Diseases, Azienda Ospedaliero-Universitaria Di Trieste, Trieste, Italia; [p]Department of Oncology, Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli, Italia; [q]Unidade De Investigação Cardiovascular (Unic), Faculdade De Medicina, Da Universidade Do Porto, Centro Hospitalar Universitário De São João, Porto, and Hospital Rainha Santa Isabel, Marco De Canaveses, Portugal; [r]Department of Clinical Investigations, Center for Genetic Engineering and Biotechnology, Havana, Cuba; [s]Qualitative Research, Helsinki, Finland; [t]Department of Anesthesiology, Volda Hospital HMR, Norway; [u]Department of Internal Medicine and Department of Biochemistry and Molecular Biophysics, ProHEALTH, an OPTUM Company, Columbia University, College of Physicians and Surgeons, USA

ABSTRACT

Background: COVID-19 has several overlapping phases. Treatments to date have focused on the late stage of disease in hospital. Yet, the pandemic is by propagated by the viral phase in out-patients. The current public health strategy relies solely on vaccines to prevent disease.

Methods: We searched the major national registries, pubmed.org, and the preprint servers for all ongoing, completed and published trial results.

Results: As of 2/15/2021, we found 111 publications reporting findings on 14 classes of agents, and 9 vaccines. There were 62 randomized controlled studies, the rest retrospective observational analyses. Only 21 publications dealt with outpatient care. Remdesivir and high titer convalescent plasma have emergency use authorization for hospitalized patients in the U.S.A. There is also support for glucocorticoid treatment of the COVID-19 respiratory distress syndrome. Monoclonal antibodies are authorized for outpatients, but supply is inadequate to treat all at time of diagnosis. Favipiravir, ivermectin, and interferons are approved in certain countries.

Expert Opinion: Vaccines and antibodies are highly antigen specific, and new SARS-Cov-2 variants are appearing. We call on public health authorities to authorize treatments with known low-risk and possible benefit for outpatients in parallel with universal vaccination.

1. Introduction

SARS-Cov-2 was first identified in December 2019 in Wuhan, China and spread with extraordinary speed. As of 15 February 2021, there have been 108,579,352 confirmed cases of COVID-19, including 2,396,408 deaths worldwide affecting 220 countries and territories [1]. Symptomatic COVID-19 exhibits a characteristic sequence of phases beginning with a primary viral attack, manifesting as an influenza-like illness. Then, within seven to 10 days of onset of symptoms, an inflammatory phase develops in up to 20% of infected individuals, typically heralded by an organizing

pneumonia [2]. In up to 5% of patients, the situation can deteriorate to a hyperinflammatory phase with acute respiratory distress syndrome. Elevated cytokines and a coagulopathy in this hyperinflammatory stage suggest an immune reaction as probable cause (Figure 1) [2–6]. Secondary infections often develop. In a number of patients who survive, a 'tail phase' ensues with prolonged disability.

In mainland China, vigorous efforts to contain the spread of COVID-19 by home isolation, mandatory masking, closure of business activity, travel bans, and tracking and control of contacts succeeded. As of 15 February 2021, China has had 101,536 confirmed cases and 4,838 deaths, but the number

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CONTACT Marc Rendell ✉ rendell@asndi.com 🔘 The Rose Salter Medical Research Foundation, Newport Coast, USA

[#]CoSenior author.

🔘 Supplemental data for this article can be accessed here.

Article highlights

• COVID-19 has characteristic phases, beginning as a viral influenza like illness which may then deteriorate to an inflammatory phase with a subsequent hyperinflammatory reaction characterized by cytokine release; Acute respiratory distress syndrome and a coagulopathy are responsible for mortality.

• The focus of treatment of COVID-19 has been on very ill hospitalized patients. Outpatients who do not require hospitalization are told to home quarantine with no effective treatment.

• The public health authorities have pursued universal immunization to prevent the disease, and several vaccines are now being administered to the population of the entire world. However, vaccination alone may not be sufficient to stop the disease as the virus continues to propagate with newly developing variants.

• We reviewed treatments now available to use in parallel with vaccination to fight COVID-19. We found a number of agents, some already approved and in use in a number of countries.

• We recommend that agents with known safety profile and preliminary evidence of possible benefit be used together with universal vaccination, while long-term studies proceed in parallel to prove efficacy.

This box summarizes key points contained in the article.

of new cases has been low since April 2020 [1]. Similar measures contained the epidemic in Taiwan and in New Zealand [1]. However, the disease has not been controlled in the rest of the World, particularly Europe where there have been 36,668,163 cases with 814,455 deaths and the United States (USA) where, despite only a fifth of the population of China, there have been 27,309,503 confirmed cases of COVID-19 and 480,464 deaths [1]. In the Western World, as in China, the response to the pandemic was through reduction of person-to-person contact. Beginning in early March, social gatherings and meetings ended; schools and businesses were closed along with recreation areas, parks, and beaches. These social distancing efforts blunted the spread of the disease, but not with the results achieved in China. Due to economic pressures, epidemiologic containment was relaxed resulting in a significant ongoing surge well surpassing the original April peak. Facing the growing crisis in early January, Chinese health authorities began treating patients empirically with agents with demonstrated in vitro antiviral activity against coronaviruses and those used during prior outbreaks of SARS 2003, H1N1 influenza of 2009 and MERS 2015 [7]. The medications included the antimalarial drugs hydroxychloroquine (HCQ) and chloroquine, the human immunodeficiency virus (HIV) protease inhibitor lopinavir-ritonavir (LPV/r), the Russian antiviral umifenovir, and traditional Chinese medical approaches [8]. Subsequently, HCQ was widely used to treat COVID-19 throughout the world, despite cautions from numerous regulatory bodies. The scientific basis for their use was in vitro evidence of an effect on blocking viral endosomal penetration, as well as a known suppressive benefit on undesirable autoimmune effects [9].

The primary current focus of treatment of COVID-19 has been on patients with disease sufficiently severe to require hospitalization. Outpatients who are diagnosed are initially told to self-quarantine at home. The major industrialized countries have made an unprecedented effort to rapidly develop vaccines to prevent SARS-Cov-2 infection. Two mRNA vaccines and several adenovirus vector vaccines have shown effectiveness at two-month post immunization, and thankfully mass vaccination has begun. However, in view of the continuing daily increase in new cases and deaths, we believe that it is unwise to rely on immunization alone. Gaining control of the pandemic depends largely on the interruption of transmission chains until protective herd immunity arises from prior cases and vaccine administration. Until that time or if acceptable levels of immunity are not reached in the community, medications will be needed for prevention and treatment of cases. Our goal was to explore the landscape of existing pharmacologic agents to prevent and treat COVID-19 while vigorously pursuing the goal of universal vaccination in 2021.
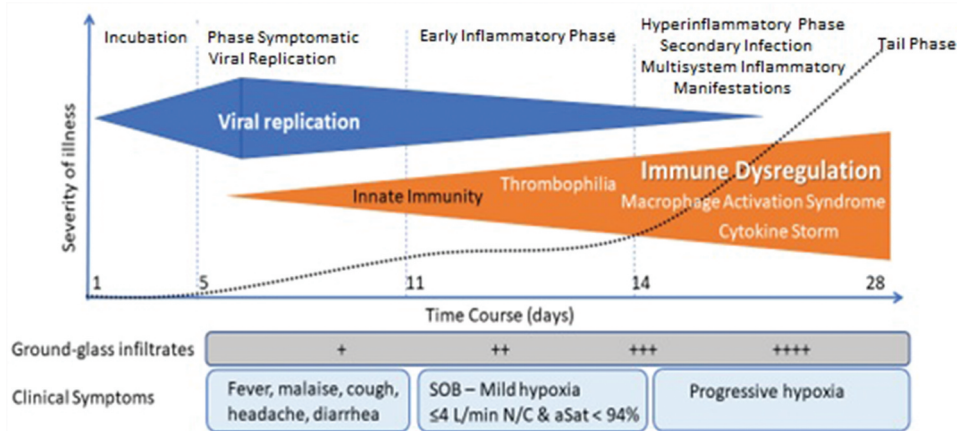

Figure 1. The Phases of COVID-19. SARS-Cov-2 infection begins with an asymptomatic period of viral incubation. As viral replication accelerates, an influenza-like illness may appear. Lung involvement begins the early inflammatory phase which can proceed to a late inflammatory phase with accompanying secondary infections and a coagulopathy. The viral load is typically falling while the inflammatory state intensifies. This phase often includes disease of multi-organ systems. Elevated cytokine levels suggest an autoimmune process as the cause. The pneumonia may lead to acute respiratory distress with severe hypoxia. In those patients who recover, there can occur a prolonged period of symptoms and disability. This "tail phase" can continue for many months.

2. Methods

2.1. Clinical trials

We reviewed up-to-date information from multiple different sources to identify potential treatments for COVID-19: The Reagan-Udall Expanded Access Navigator COVID-19 Treatment Hub was used to track the efforts of companies to develop therapeutic interventions. We actively searched for agents thus identified. We further searched for investigational trials for COVID-19 in active recruitment and those that have completed enrollment. We used (A) covid-trials.org, a registry to collate all trials in real time with data pulled from the International Clinical Trials Registry Platform and all major national registries [10]. We cross validated this information on (B) clinicaltrials.gov, the registry of clinical trials information maintained by the United States National Library of Medicine and further cross-referenced the trials on C) the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), and (D) (Cochrane COVID-19 Study Register. We excluded studies which were clearly observational with multiple different treatments, with no means of comparison. We further set a cutoff of 100 for numbers of subjects since smaller trial size typically lacks statistical power to enable regulatory approval. For each trial selected, we documented the setting of patient contact, either hospital or outpatient, the type of control procedure, the date the trial was initially registered, and the proposed date of completion of enrollment.

2.2. Published trial results

Our search was carried on the week of 1 February 2021. We identified all publications on pubmed.gov to find peer reviewed articles, on medRxiv to find preprint reports and the WHO Global Literature on Coronavirus Disease. We further carried out daily Google™ searches on each potential treatment to find preliminary reports, typically presented as press releases, reviewed by a journalist. We included all publications in our results as well as trial results posted as complete on Clinicaltrials.gov. We did not exclude trials with less than 100 subjects, since many reports were interim, with trials ongoing.

2.3. Virtual discussions among coauthors

We used the preprint server medRxiv to post a systematic analysis of the development of therapeutic interventions for COVID-19 in order to stimulate diffusion of the manuscript and allow widespread 'open source' input from coauthors [11,12]. Successive versions of the preprint article have been posted periodically as a chronicle beginning in late May 2020 and continuing to date. This process led to the present multinational consensus process.

3. Results

3.1. Review of current trials

As of 1 February 2021, we identified 835 trials currently in recruitment phase with subject size of 100 or more. These trials have been listed as a Supplementary Table S1 in our preprint article [12]. Of these, 150 were directed at prevention in healthy individuals, 126 were classified as treatment of outpatients with documented infection, and 487 were for treatment of hospitalized inpatients. There were 11 trials focusing on the post-discharge Tail phase. The remaining trials were unclear or mixed as to intended subjects. Among the trials, there were 79 vaccine trials, 151 trials involving hydroxychloroquine (HCQ), 41 trials of alternative therapy, 15 trials of colchicine, 48 trials of anticoagulants, 25 trials of the intravenous RNA polymerase inhibitor remdesivir and 23 trials of the oral RNA polymerase inhibitor favipiravir (FVP), 21 trials of interferons, 25 trials of glucocorticoid, and 69 trials of plasma-based products

3.2. Completed trials

As of February 1,2021, there were 104 trials reporting completion with 100 or more subjects. These trials have been listed as Supplementary Table 2 in our preprint article [12]. There were 65 trials in hospitalized patients, 9 directed at outpatients, and 13 prevention studies, rest unclear.

3.3. Published results on COVID-19 trials

As of 15 February 2021 we found 111 publications reporting findings in human studies on 14 classes of agents, and on 9 vaccines. There were 62 randomized or active controlled studies. The rest were retrospective observational analyses. Only 21 publications dealt with outpatient care, including 9 vaccine reports; the rest were all in hospitalized patients. We have listed certain key studies with high potential impact in Table 1

3.3.1. Antiviral agents

3.3.1.1. Remdesivir. In the group of antiviral agents, the largest published randomized, controlled trials were with the intravenously administered RNA polymerase inhibitor remdesivir [13–17]. An initial double-blind randomized study on 237 patients in China showed no benefit on viral clearance nor mortality (13, Table 1). A double-blind, randomized placebo-controlled trial of remdesivir, in 1062 moderate to severely ill patients was carried out by the National Institute of Allergy and Infectious Disease (NIAID) (14, Table 1). The patients who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P < 0.001). P < 0.001). The Kaplan-Meier estimates of mortality by 29 days after randomization were 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). On the basis of this trial, the Food and Drug Administration (FDA) approved the use of remdesivir for COVID-19 hospitalized patients. A different study of remdesivir in hospitalized patients with moderate COVID-19 clinical status showed improved clinical status by day 11 compared to standard of care for a 5-day course of remdesivir, but not for a 10-day course [15]. There has been no data provided on viral clearance for the U.S. remdesivir studies. In early April, 2020, the

Table 1. Published studies of high impact as of 15 February 2021. Each agent is listed along with the country originating the publication. We have listed studies with 100 or more subjects. The type of control procedure: RCT: Randomized controlled study PLAC: Placebo, soc: standard of care which is variable depending on each location. AC: Active control: the control options are listed in parenthesis. OBS: retrospective observation study. LPV/R: lopanavir/ritonavir; HCQ: hydroxychloroquine; AZM: azithromycin; IFN: interferon; toclizumab:TCZ. SEV: severe; CRIT: critical; MOD: moderate. WHO: World Health Organization.

TREATMENT	LOCATION	TYPE OF CONTROL	NUMBER SUBJECTS	SETTING	SEVERITY	RESULTS
Remdesivir[13]	China	RCTPLAC vs soc	273	HOSP	SEV	mortality in remdesivir group 14%, control 13% 11% in remdesivir group with <10 days symptoms Vs 14% in placebo group, no difference in viral clearance
Remdesivir[14]	U.S.A.	RCTPLAC	1062	HOSP	SEV,CRIT	29 day mortality 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03)
Remdesivir[17]	W.H.O.	AC(10 day, vs soc)	5451	HOSP	MOD,SEV	Mortality Remdesivir RR = 0.95 (0.81–1.11, p = 0.50 301/2743 active vs 303/2708 control
FVP[19]	China	AC (umifenovir vs favipiravir)	240	HOSP	MOD,SEV	Clinical recovery rate 56%umifenovir vs 71% fvp
HCQ[24]	France	OBS(hcq+azm, noncomparable control group)	3737	MIXED	MILD,MOD	0.9% overall mortality, no sudden death, no cardiac arrythmias
HCQ[38]	U.K.	RCT (HCQ vs soc)	1542	HOSP	MOD,SEV	no significant difference in28-day mortality (26.8% hydroxychloroquine vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96–1.23]; p = 0.18) (Mortality RR = 1.19 (0.89–1.59, p = 0.23; 104/947 HCQ vs 84/906 control
HCQ[17]	W.H.O.	AC(HCQ vs soc)	1853	HOSP	MOD, SEV	Mortality RR = 1.19 (0.89–1.59, p = 0.23; 104/947 HCQ vs 84/906 control
HCQ[39]	U.S.A.	OBS (hcq+azm +zinc vs hzq +azm)	932	HOSP	MOD,SEV	Reduction in mortality with addition of Zinc OR 0.449, 95% CI 0.271–0.744).
HCQ[42]	Spain	RCTPLAC	293	OUTPAT	MILD	no difference in viral load at 7 days after 6 days HCQ treatment nor risk of hospitalization compared to untreated patients
HCQ[43]	Spain	RCTPLAC	2324	OUTPAT	HEALTHY	no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54–1.46]), nor evidence of prevention of SARS–CoV-2 transmission (17.8% usual care vs. 18.7% HCQ)
HCQ[46]	Canada	RCTPLAC	1483	OUTPAT	HEALTHY	3 month treatment with HCQ in hospital workers no significant difference in SARS-Cov-2 infection rate HCQ 0.27 events per person/year vs placebo 0.38% (p = 0.18)
LPV/r[49]	U.K.	RCT(soc)	1596	HOSP	MOD,SEV	no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91–1.18];(p = 0.58)
LPV/r[17]	W.H.O.	AC(LPV/r vs soc)	2771	HOSP	MOD,SEV	Mortality LPV/r (RR = 1.00 (0.79–1.25, p = 0.97; 148/1399 vs 146/1372
LPV/r[50]	Hong Kong	AC(lpv/r+ ribavirin+beta interferon vs lpv/r+ ribavirin)	127	HOSP	MOD,SEV	Triple combination of interferon beta-1b, lpv/r, and ribavirin yielded more rapid viral clearance but attributable primarily to interferon
IFN[17]	W.H.O.	AC(vs soc)	4100	HOSP	MOD,SEV	Mortality IFNRR = 1.16 (0.96–1.39, p = 0.11; 243/2050 vs 216/2050)
IFN-α nasal drops[54]	China	OBS	2944	OUTPAT	HEALTHY	No cases of COVID-19 compared to historical control
IFN- β-1a(nebulized)[56]	U.K.	RCT(soc)	101	HOSP	MOD,SEV	OR for clinical improvement 2 . 32 (1 · 07–5 · 04)
Convalescent plasma[57]	China	RCT(soc)	103	HOSP	SEV,CRIT	time to clinical improvement at 28 days was 4.9 days shorter (95% CI, −9.33 to −0.54 days) in convalescent plasma group (HR, 2.15 [95% CI, 1.07–4.32]; P = .03). No significant difference in critically ill patients.
Convalescent plasma[62]	U.S.A.	OBS	3,082	HOSP	MOD,SEV	Mortality 28-day mortality (15.7% convalescent plasma vs 24.0% control; P = .30) adjusted 30–35 day mortality was 30% in patients treated with plasma with low antibody levels (IgG) 35 or more days after COVID-19 diagnosis. By contrast 30-day mortality was 20% in 353 patients treated within 3 days of diagnosis with plasma with high antibody levels.
Convalescent plasma[63]	U.S.A.	OBS	160	HOSP	MOD,SEV	severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03).
Convalescent plasma[64]	U.S.A.	OBS	21,987	HOSP	MOD,SEV	7 day mortality 13%
LY-CoV555[66]	U.S.A.	RCT(soc)	452	OUTPAT	MILD,MOD	6.2% of patients receiving placebo had emergency room visit or hospitalization vs 1.6% patients who received antibody
RGN-Cov2[67]	U.S.A.	RCT(soc)	275	OUTPAT	MILD,MOD	Decreased viral load vs placebo; 6% medical visits for placebo patients vs 3% for those receiving monoclonal antibody cocktail
Fluvoxamine[70]	U.S.A.	RCT(fluvoxamine vs soc)	152	OUTPAT	MILD,MOD	Clinical deterioration in 0 patients on fluvoxamine, 8.7% placebo (p < 0.009)
Ivermectin[71]	India	Case Control (ivermectin vs placebo)	115	OUTPAT	HEALTHY	Two doses of ivermectin yielded 73% reduction in COVID_19 cases
Dexamethasone[79]	U.K.	RCT(soc)	6119	HOSP	MOD,SEV	Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p < 0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p = 0.002

Table 1. (Continued).

TREATMENT	LOCATION	TYPE OF	NUMBER	SETTING	SEVERITY	RESULTS
Methylprednisolone[80]	Italy	RCT(soc)	173	HOSP	SEV	Methylprednisolone group had fewer deaths (6 vs. 21, adjusted HR = 0.29; 95% CI: 0.12–0.73) and more days off invasive mechanical ventilation (24.0 ± 9.0 vs. 17.5 ± 12.8; p = 0.001)
Anakinra[104]	Greece	OBS(vs soc)	130	HOSP	SEV	Incidence of severe respiratory failure 22% anakinra patients vs 59% soc,, 30 day mortality 11.5% anakinra vs 22.3% soc).
TCZ[111]	U.S.A.	RCTPLAC (TCZvs soc)	803	HOSP	SEV,CRIT	Mortality 28% tocilizumab vs 36% control
TCZ[112]	U.K.	RCTPLAC (TCZvs soc)	4116	HOSP	SEV,CRIT	Mortality 29% tocilizumab vs 33% control
Colchicine[115]	Greece	RCT(colchicine vs soc)	105	HOSP	MOD,SEV	The clinical primary end point rate was 14.0%in the control group (7 of 50 patients) and 1.8%in the colchicine group (1 of 55 patients) (odds ratio,0.11; 95%CI, 0.01–0.96; P = .02).
Colchicine[116]	Canada	RCT(colchicine vs soc)	4159	OUTPAT	MILD,MOD	The clinical primary end point rate was 6% in the control group and 4% in the colchicine group ((odds ratio, 0.75; 95% CI, 0.57 to 0.99; P = 0.04)
Mesenchymal Stem Cells[120]	China	RCTPLAC	101	HOSP	SEV WITH LUNG DAMAGE	Lesion volume decreased compared to placebo (p < 0.05)

WHO organized a megatrial, appropriately named Solidarity, to assess four separate treatment options only in hospitalized patients: (a) Remdesivir; (b) The HIV agent lopinavir/ritanovir (LPV/R); (c) LPV/R plus Interferon β-1a; and (d) the antimalarials hydroxychloroquine (HCQ) and chloroquine [17]. Results of the Solidarity Trial were initially reported by the World Health Organization on 15 October 2020. They found no effect of remdesivir on 28-day mortality, need for mechanical ventilation nor duration of hospitalization in a study including 5451 hospitalized patients (17, Table 1).

3.3.1.2. Favipiravir. There were two positive randomized, active control clinical trials in China of the orally administered RNA polymerase inhibitor favipiravir (FVP) [18,19]. In a trial comparing 116 patients on FVP to 120 on umifenovir, the 7-day clinical recovery rate was 55.9% for the umifenovir group and 71% in the FVP group (19, Table 1). In Japan, a clinical registry containing 1918 hospitalized patients receiving FVP on a compassionate use basis was released on 2 June 2020 [20]. There was no control group nor data on viral clearance. Patients were treated on average 3 days post admission to the hospital. The 30-day overall mortality was 11.6%. In Russia, a preliminary study of FVP showed reduced duration of viral shedding, and the drug was approved for clinical treatment beginning in multiple hospitals on 12 June 2020 [21]. In a follow-up phase 3 study, they reported 27% clinical improvement at day 10 compared to 15% for standard care with 98% clearance of SARS-COV-2 compared to 79% [22]. In India, a study of 150 mild to moderate COVID-19 patients showed median time to clinical cure of 3 days (95% CI: 3 days, 4 days) for FVP versus 5 days (95% CI: 4 days, 6 days) for control, P = 0.030, and FVP received approval in July 2020 to treat COVID-19 [23]. In late September, a report, still unpublished, of a randomized controlled study in Japan announced more rapid viral clearance in FVP treated patients.

3.3.1.3. Hydroxychloroquine. There have been many studies of HCQ [24–51]. A group in Marseille reported their experience with 3737 patients screened positive for SARS-Cov-2 and immediately treated with HCQ and azithromycin (AZM), after excluding patients at risk of QT prolongation (24, Table 1). They showed clearance of viral shedding in 89.4% of the patients by 10 days. The overall mortality in their population was 0.9%, none in patients under 60 years old, and no sudden cardiac deaths. They had no randomized control population, but their study prompted immediate widespread use of HCQ throughout the world for treatment of COVID-19 patients.

Most subsequent observational or randomized controlled studies in hospitalized patients have shown no clinical nor mortality benefit of HCQ. In the randomized RECOVERY trial in 1542 hospitalized patients in the United Kingdom, there was no significant difference in the primary endpoint of 28-day mortality (26.8% HCQ vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96–1.23]; p= 0.18) (38, Table 1). In the Solidarity Trial, there was no benefit of HCQ on mortality (HCQ RR = 1.19 (0.89–1.59, p = 0.23; 104/947 vs 84/906), need for mechanical ventilation, nor duration of hospitalization (17, Table 1). However, in a retrospective comparison study at NYU Langone Health for all patients admitted between 2 March and 5 April 2020, there was a move to add zinc

100 mg daily to their standard HCQ plus AZM regimen (39, Table 1). There was a significantly lower mortality (13.1%) among the zinc treated patients compared to those who did not receive zinc (22.8%).

There has been limited study of HCQ in outpatients. In one internet-based prevention study, with HCQ given for 5 days to healthy individuals with a significant exposure to SARS-Cov-2, the incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving HCQ (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); absolute difference −2.4 percentage points (95% confidence interval, −7.0 to 2.2; p= 0.35) [40]. The same group also treated 423 patients with mild symptoms imputed to COVID-19 [41]. At 14 days, 24% (49 of 201) of participants receiving HCQ had ongoing symptoms compared with 30% (59 of 194) receiving placebo (p = 0.21).

A study in Spain of 293 patients with PCR-confirmed mild COVID-19, found no difference in viral load nor risk of hospitalization following 6 days HCQ treatment compared to untreated patients (42, Table 1). The same group treated 1,116 healthy contacts of 672 Covid-19 index cases with HCQ while 1,198 were randomly allocated to usual care (43, Table 1). There was no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54–1.46]) nor evidence of prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ).

A large population study in Portugal surveyed all patients on chronic HCQ treatment and cross-verified against a mandatory database of patients registered with COVID-19 [44]. The incidence of a positive PCR test for SARS-CoV-2 infection in patients receiving HCQ was 5.96%, compared to 7.45% in those not so treated, adjusted odds ratio 0.51 (0.37–0.70). However, two separate randomized controlled studies found no evidence of benefit of two months prophylactic treatment of hospital workers with HCQ (45,46, Table 1).

3.3.1.4. Lopinavir/ritonavir.
Published results with Lopinavir/ritonavir (LPV/r) have been disappointing [17,47–50]. In a randomized trial with 99 patients on LPV/r and 100 receiving standard care, there was no difference in time to clinical improvement, mortality nor viral clearance [48]. In the RECOVERY trial in 1,596 hospitalized patients there was no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91–1.18]; (p= 0.58) (49, Table 1). In the Solidarity Study, there was no effect of LPV/r on 28-day mortality LPV/r RR = 1.00 (0.79–1.25, p = 0.97; 148/1399 vs 146/1372), need for mechanical ventilation nor duration of hospitalization (17, Table 1).

A possibly more favorable result was obtained in Hong Kong in a study of 86 patients assigned to triple combination therapy with LPV/r plus ribavirin plus interferon β-1 (50, Table 1). Compared to a control group of 41 patients receiving LPV/r alone, the combination group had a significantly shorter median time from start of study treatment to negative SARS-Cov-2 nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–-10.24], p= 0 · 001). The time to complete alleviation of symptoms was 4 days [IQR 3–8] in the combination group vs

8 days [7–9] in the control group; HR 3.92 [95% CI 1.66–9.23]. This study was interpreted not as supporting LPV/r therapy, but rather focusing on interferon β-1 as the primary treatment modality.

3.3.1.5. Interferons.
Several interferon studies have been more encouraging [51–56]. In Cuba, a combination of interferon-α-2b and interferon γ on background therapy of LPV/r and chloroquine was successful in achieving viral clearance in 4 days in 78.6% of the patients compared to 40.6% of those receiving interferon-α-2b alone [53]. A trial of prophylactic nasal interferon in 2944 Chinese health workers demonstrated no cases compared to a historical control population (54, Table 1). In the Solidarity Study in hospitalized patients, there was no effect of injected interferon on 28-day mortality (IFN RR = 1.16 (0.96–1.39, p = 0.11; 243/2050 vs 216/2050), need for mechanical ventilation nor duration of hospitalization (17, Table 1). However, a trial of nebulized interferon β-1 in the U.K. reported positive improvement in clinical status (56, Table 1).

3.3.1.6. Passive immunization.
Infusion of COVID-19 convalescent plasma has yielded mixed results [57–63]. A trial in China of 103 patients did not achieve its primary endpoint before termination due to declining number of cases [57]. A study of 464 patients in India showed no benefit in progression to severe disease nor all cause mortality at 28 days after enrollment [58]. However, several studies quantitating antibody titers suggest a reduction of mortality of 50% in patients treated within 3 days of diagnosis with high titer plasma (62,63, Table 1). Based on evidence of safety in over 20,000 patients in an expanded access program coordinated by the Mayo Clinic, the U.S. FDA issued an emergency authorization for use of convalescent plasma [64]. Passive immunization in the early viral replication phase of COVID-19 has been further pursued with synthetic monoclonal antibodies to the SARS-COV-2 spike protein. Treatment of ambulatory patients with the LY-CoV555 neutralizing antibody and the Regeneron combination of two antibodies early in the course of infection but not later has shown success in reducing the frequency of hospitalization, and the FDA issued an emergency authorization for use in outpatients (65–67, Table 1).

3.3.1.7. Agents not usually considered antivirals.
There have been a number of favorable reports on agents not ordinarily considered as antivirals. These include famotidine, nitazoxanide, fluvoxamine, and ivermectin [68–75]. A small randomized control study of fluvoxamine in outpatients showed no clinical deterioration versus 8.7% placebo [70]. There have now been a number of trials including several randomized controlled studies suggesting benefit with ivermectin both in prevention and in treatment of COVID-19 [75]. In a matched case control study in India ivermectin prophylaxis yielded a 73% reduction in infection of health-care workers [71]. Ivermectin has now been authorized as treatment in several countries.

3.3.2. Immunomodulatory treatment
3.3.2.1. Glucocorticoids.
There have been many observational studies of immunomodulatory therapy for the

Table 2. SARS-Cov-2 vaccines either currently or soon to be authorized.

Vaccine	Commercial sponsor	Country	Vaccination Schedule	Vaccine Technology	Reported Effectiveness	Authorization for Use
BNT162b2 [122]	Pfizer/Biontech	U.S.A.	2 shots	mRNA	95%	U.S.A., European Union, U.K., Israel
mRNA1273 [123]	Moderna	U.S.A.	2 shots	mRNA	94%	U.S.A, U.K. E.U.
Sputnik 5 [124]	Gamelaya Institue	Russia	2 shots	Adenovirus vector	91%	Russia
CHadOx1 [125]	Astra Zeneca	U.K.	2 shots	Adenovirus vector	70%	U.K., E.U.
Ad5-nCoV [126]	Cansino	China	One shot	Adenovirus vector	66%	China
Ad26.COV2.S [127]	Janssen	U.S.A.	One shot	Adenovirus vector	72%	South Africa
NVX-CoV2373 [128]	Novavax	U.S.A.	Two shots	Recombinant spike protein	89%	– – – –
BBIP B-CorV [129]	Sinopharm	China	Two shots	Alum precipitated inactivated virus	86%	China, Bahrain, United Arab Emirates, Egypt
Coronavac [130]	Sinovac	China	Two shots	Inactivated virus	50%	China, Brazil
Covaxin [131]	Bharat Biotech	India	2 shots	Inactivated virus	– –	India

inflammatory and hyperinflammatory phases of COVID-19. Pre-COVID-19, glucocorticoid treatment had been a recognized treatment with mortality benefit for acute respiratory distress syndrome [76–78]. Dexamethasone has now demonstrated benefit in several COVID-19 hospital trials [79,80]. In the RECOVERY trial, 2104 patients were randomly allocated to receive dexamethasone for 10 days compared to 4321 patients concurrently allocated to usual care (79, Table 1). Overall, 454 (21.6%) patients randomized to dexamethasone and 1065 (24.6%) patients receiving usual care died within 28 days (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; p < 0.001). Dexamethasone reduced deaths by one-third in the subgroup of patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p < 0.001) and by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p = 0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs.13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p = 0.14). Most trials of other glucocorticoids have shown similar benefits in COVID-19 patients with acute respiratory failure [80–87]. Methylprednisolone, in particular, has been successful in reducing mortality (80, Table 1). There has been ongoing concern about potential harm of suppression of the immune response by utilizing glucocorticoids during the early viral replication phase of COVID-19. High viral load is associated with greater risk of respiratory deterioration and mortality [88]. However, it was recently shown that inhaled budesonide was beneficial in cases of early mild COVID19 (89, Table 1). To be sure, the initial viral load in these patients was fairly low (Mean Ct 32).

3.3.2.2. Anti-cytokine antibodies.
Many observational studies of targeted anti-cytokine treatment with the IL-6 inhibitors tocilizumab and sarilumab, the GM-CSF inhibitor mavrilimumab, and the IL-1 inhibitor anakinra suggested reduction of mortality and need for intubation in the hyperinflammatory phase of COVID-19 [32,87–106]. However, several randomized control studies showed no apparent benefit with tocilizumab nor with sarilumab [107–109]. In the COVACTA trial, there was no benefit of tocilizumab in clinical status, mortality (19.7% tocilizumab vs placebo = 19.4%) nor in ventilator-free days [108], and in the Cor-Immuno-Toci trial, no

decrease in mortality at day 28 [109]. Sarilumab studies were ended early after an interim analysis failed to show benefit [110]. However, the results in these randomized controlled trials were confounded by a higher frequency of glucocorticoid use in the control groups. The REMAP-CAP Study was performed after general acceptance of glucocorticoid treatment for severely ill COVID-19 patients. In their cohort, of whom 93% were steroid treated, there was clear superiority of tocilizumab and sarilumab in organ support free days, time to discharge and 90-day mortality (111, Table 1).Similarly, the RECOVERY TRIAL recently reported that tocilizumab treatment reduced mortality from 33% to 29% in a cohort of patients of whom 82% were receiving glucocorticoids (112, Table 1).

3.3.2.3. Colchicine.
Early studies of colchicine pointed to a beneficial effect in both hospitalized and ambulatory patients [113,114]. In the GRECCO, placebo-controlled, randomized clinical trial of 105 hospitalized patients, the primary clinical end point of deterioration to mechanical ventilation or death was 14% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01–0.96; p = 0.02) (115, Table 1). The ColCorona study recently reported on 4159 outpatients with PCR-confirmed COVID-19; the primary endpoint of hospitalization or death occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (odds ratio, 0.75; 95% CI, 0.57 to 0.99; P = 0.04) (116, Table 1).

3.3.2.4. Stem cells.
In patients who recover from COVID-19 respiratory failure, there is often a prolonged tail phase of slow recovery, with lingering shortness of breath and decreased exercise tolerance. There have been several pilot studies suggesting initial benefit with introduction of mesenchymal stem cells into the lungs during the inflammatory and hyperinflammatory phases of COVID-19 [111–115]. In a small randomized control study comparing 12 patients who received umbilical cord-derived stem cells with 12 who receive placebo, there was improved survival (92% vs 42%) in the stem cell group (117–121, Table 1).

There are currently more than 60 vaccines in clinical development worldwide. Nine vaccines are either authorized or shortly will be (122–131,Table 2). The Moderna and Pfizer Biontech mRNA spike protein vaccines released phase 3 data

showed 95% effectiveness at preventing symptomatic infection in a 2 month post-immunization observation period, and emergency authorization for immunization has been given in many countries. These vaccines have relatively stringent temperature requirements for transport and storage. Recombinant adenovirus vectored vaccines, one nanoparticle protein vaccine and several inactivated virus vaccines have also demonstrated protection in short-term studies. Large-scale vaccination programs are underway in the United States, the United Kingdom, India, Russia, China, and the European Union. At the same time, a different approach was suggested to stimulate nonspecific immunity using oral polio or BCG vaccine [132]. None of these studies of nonspecific immunizations has yet reported results.

4. Conclusion

SARS-Cov-2 fueled by modern day jet travel overwhelmed medical preparedness for the pandemic. Current projections are for a continuation of new cases and deaths continuing in 2021 [133,134]. Clinical trials to date have targeted predominantly hospitalized patients to try to prevent death. It is hoped that the use of remdesivir, convalescent plasma, glucocorticoids, specific immunomodulator therapy, and anticoagulation will lower the present rate of in hospital mortality which in some series has been as low as 6% but in most hospitals still approaches 20% [83]. However, it is essential to change the present dynamic of attempted therapeutic responses to recognize and treat the specific phases of the disease that our group has previously defined [2,135]. In particular, efforts must now focus on prevention and treatment of the initial viral infection so that hospitalization can be avoided. We face a dilemma with inadequate current prevention and treatment for outpatients with mild to moderate disease, constituting 80% of the infected population and the primary mode of spread of SARS-Cov-2. The lessons learned in very sick hospitalized patients do not necessarily apply to the earlier viremic phase. Antiviral agents, such as remdesivir and favipiravir, interferon, convalescent plasma, and monoclonal antibodies are likely to be most effective during the early stage of viremia, which is prior to the inflammatory pulmonary phase requiring hospitalization.

There has been very little emphasis on outpatient antiviral trials. Vaccines have been the solitary hope held out by public health authorities to arrest SARS-Cov-2. Progress on vaccine development has been rapid, but the speed of development does not reduce the challenges of developing a vaccine to be administered to the population of the entire World. Although neutralizing antibodies and memory T cells can be produced by the vaccine candidate, the demonstration of true protection requires long-term follow-up of an exposed vaccinated population. The current vaccines are released for emergency use after only a short 2-month period of observation. No matter how rapidly a vaccine advances to Phase III testing, the duration of follow-up cannot be shortened, and for SARS-Cov-2 possibly prolonged due to several factors. First, there is a risk of immune enhancement of infection which occurs when induced antibodies increase entry and internalization of virus into myeloid cells [136]. This major complication struck the newly developed dengue vaccine in 2017 [137]. Second, the sinister autoimmune pathogenicity of SARS-Cov-2 raises the risk of delayed long-term harm if the virus is not fully and immediately eradicated by the initial immune response to the vaccine. Furthermore, studies of recurrent coronavirus infections suggest that infection may confer immunity for less than a year [138]. Vaccines are highly specific to targeted antigens. There is the risk that the virus will mutate to a form for which the new vaccine may not be fully protective. Already, a number of variants have emerged and caused major outbreaks [139,140]. The incidence of possible reinfection by the Brazilian P1 variant in Manaus has raised great concern [141].

After release of the current vaccines, efforts to find volunteers for trials of new, more effective vaccines will be hampered if there is no treatment available for placebo treated patients who become infected. Finally, the degree of acceptance of the COVID-19 vaccines by the general population is questionable. Seasonal influenza vaccination coverage was only 48% in 2019 [142]. Children typically have limited COVID-19 symptoms. However, they may serve as a reservoir of ongoing infectivity [143]. Currently there have been no clinical trial results of vaccine in children.

5. Expert opinion

It also follows that totally new viruses may emerge just as did SARS-Cov-2. COVID-19 is now the sixth severe viral epidemic to hit mankind in the past 20 years; certainly, it has been more widespread than SARS-Cov-1, H1N1 influenza, MERS, Zika, and Ebola, but that does not diminish the gravity of these repeated viral threats. Development of antigen-specific vaccines takes a long time during which disease takes a large toll as has been the case for SARS-Cov-2. The succession of viral afflictions points to the need to implement widespread use of antiviral agents. The current recommendation for COVID-19 is home quarantine with no specific treatment for patients with suspicious symptoms. What is needed is therapeutic intervention which can be used to treat all outpatients with positive COVID-19 tests at the time of initial symptoms, not waiting for deterioration requiring hospital care. Hydroxychloroquine has not succeeded. Remdesivir administered intravenously for 5 days is not a practical daily outpatient treatment; Gilead© is attempting to develop an inhaled remdesivir formulation, but those efforts are only now beginning. Favipiravir, a tablet, could be used in early stages of infection and has now been released in Russia, Hungary, and in India, but not in the United States and the European Union. It has known embryogenic risks, so its use requires restrictions on women of childbearing potential, as is the case with isotretinoin for acne and thalidomide for multiple myeloma. Convalescent plasma is used primarily in hospital patients. Monoclonal antiviral neutralizing antibodies have received emergency use authorization for ambulatory patients. However, the scale of production of these monoclonal antibodies is far too limited to offer to all outpatients. Interferon formulations have shown promise in several studies. Colchicine has successfully mitigated the course of COVID-19 in the ColCorona Study. There have been several randomized controlled studies suggesting benefit with ivermectin both for prophylaxis and treatment.

Yet, at this time, no outpatient therapy has been absolutely proven safe and effective in large-scale phase III randomized, placebo-controlled studies. There are strong arguments to avoid emergency use of agents until trials are completed and analyzed, but the agents suggested are not new. Most are drugs like zinc, ivermectin, colchicine, inhaled glucocorticoids, and the interferons, marketed and available for other conditions and with well-known safety profiles. There is a clear need to offer outpatient therapeutic intervention now to the World population. It is also imperative to treat COVID-19 specific to the disease phase. Antiviral treatments are appropriate during the incubation and viremic period. They are not necessarily beneficial during the inflammatory and hyperinflammatory phases. Just as glucocorticoids and anti-cytokine treatment could be potentially harmful during the phase of viral replication. In Figure 2, we have outlined a schematic of potential phase-specific treatment.

We should remember that the greatest success in fighting a pandemic occurred over the past two decades in the battle against the HIV which causes AIDS. AIDS was first recognized in 1981 in the MSM (men who have sex with men) community [144]. The disease was considered a death sentence. There was

widespread fear because there was no treatment, and projections of infection escalated into the millions. The first AIDS remedy was azidothymidine (AZT), synthesized in 1964 in the hope that it would combat cancer. Twenty years later Dr. Samuel Broder, head of the National Cancer Institute, showed that the drug had activity against the HIV virus in vitro [145]. Burroughs Wellcome launched a rapidly conceived trial with just 300 patients. They stopped the trial in 16 weeks claiming that more patients survived on AZT. The FDA came under enormous pressure from AIDS activists to make the drug available, and it was approved on 19 March 1987, with only that one trial. It had taken 20 months for the FDA to give approval to release the drug. To this day, the design and results of the trial remain controversial.

The LGBT community continued to battle for early release of other medications to combat the AIDS pandemic. On 11 October 1988, a massive protest occurred at the FDA. It was back then Dr. Anthony Fauci who publicly advanced the idea of a parallel track to make drugs widely available even while studies are progressing: *'Clearly, the standard approach to the design of clinical trials – that is, rigid eligibility criteria as well as the strict regulatory aspects that attend clinical trial investigations and drug approval – was not well-suited to*

Time Period	Pre-Exposure Period	Incubation Period (post exposure)	Viral Replication Period	Inflammatory Period	Hyperinflammatory Period	Tail Phase
Phase Specific Treatment -->	ANTIVIRAL	ANTIVIRAL	ANTIVIRAL	ANTI-INFLAMMATORY, ANTICOAGULANT	ANTI-INFLAMMATORY, ANTICOAGULANT, ANTIBACTERIAL	ANTI-INFLAMMATORY, ANTICOAGULANT
Administration			Remdesivir	Glucocorticoid	Glucocorticoid	Glucocorticoid
INTRAVENOUS		Monoclonal Antibodies	Monoclonal Antibodies Interferon alpha, beta, gamma Convalesscent Plasma	Anti-cytokine agents Heparin	Anti-cytokine agents Heparin Antibiotics Mesenchymal Stem Cells	Anti-cytokine agents Heparin Antibiotics Mesenchymal Stem Cells
INJECTION	VACCINES	Interferon alpha, beta, gamma				
ORAL	Zinc Ivermectin	Favipiravir Zinc Ivermectin	Favipiravir Zinc Ivermectin	Ivermectin Colchicine Glucocorticoid	Ivermectin Conchicine	
INHALATION		Interferon beta	budesonide for mild infections Interferon beta	Budesonide		

INHALATION
INHALATION

Figure 2. Phase-specific treatment of COVID-19. The successive disease periods call for different treatments. Antiviral treatments, including convalescent plasma., monoclonal antibodies, and interferons are indicated during the period of viral replication, but are unlikely to be effective during the inflammatory process. Suppression of the immune response is indicated to combat the inflammatory events.

a novel, largely fatal disease such as this with no effective treatments, and we had many intense discussions about how to make that approach more flexible and ethically sound. One example, which I and others worked closely with the AIDS activists to develop, was called a parallel track for clinical trials. The parallel track concept, which the United States Food and Drug Administration ultimately came to support, meant that there would be the standard type of highly controlled admission criteria and data collection for the clinical trial of a particular drug. In parallel, however, the drug also could be made available to those who did not meet the trial's strict admission criteria but were still in dire need of any potentially effective intervention, however unproven, for this deadly disease' [146].

The parallel track advocated by Dr. Fauci was adopted. Today, there are 41 drugs or combinations approved by the FDA to treat and to prevent HIV infection. There is still no vaccine. There are now an estimated 1.1 million patients with HIV in the United States, most enjoying near normal life expectancy thanks to the antiviral agents. The CDC has contributed greatly to limit the spread of HIV by advocating safe sex practices, but social distancing is not the norm for HIV. Rather 'treatment as prevention' for people with HIV using highly active antiretroviral regimens to prevent transmission as well as pre-exposure prophylaxis with a daily antiviral combination pill are currently endorsed by the CDC and adopted in wide segments of the at risk population [147].

In this pandemic crisis, we appeal to public health authorities to change the dynamic to outpatient care to use agents with low-risk and potential benefit like inhaled glucocorticoids, ivermectin, interferon, favipiravir, and colchicine. There is also promising data on several investigational agents including molnupiravir, cysteine protest inhibitors, mTORC inhibitors, and CD24Fc agents [148–155]. There must be a collective effort to cross institutional, commercial and international boundaries to collate and combine all randomized controlled data submitted for all new agents in Europe, China, Russia, Japan, India and other countries, and by competing companies, whether officially published, posted on line, or unpublished to finalize confirmatory results. The Solidarity Trial is a model of what could and should be done to unify a worldwide effort to pursue randomized controlled studies in outpatients. At the same time, agents with favorable preliminary results and no safety issues should be made immediately available through a parallel track. In Russia and India, the parallel track has been fully implemented, with FVP now offered as treatment throughout both countries, even as further confirmatory controlled trials proceed. Interferon formulations are now approved treatments in China and Cuba. At this time, with no other option available, vaccination must be rapid and universal, despite the need to perform controlled studies to develop improved vaccines. However, it is unwise to rely solely on the hope for eventual mass vaccination to stop SARS-Cov2. Antiviral medication has succeeded in limiting HIV and hepatitis, and antivirals are just as important as annual vaccination for control of influenza. It is necessary for public health authorities to make hard decisions now despite limited current data and offer outpatient treatments on a broad front with no further delay.

Declaration of interest

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ORCID

Ivan Fn Hung http://orcid.org/0000-0002-1556-2538

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