Supplementary Appendix

Supplementary Methods

Selection criteria

We enrolled adult patients who were hospitalized with PCR-confirmed COVID-19, as determined by a positive SARS-CoV-2 RT-PCR on any biological sample.

The full list of inclusion and exclusion criteria was the following.

Inclusion criteria:

- Adult ≥18 years of age at time of enrolment;
- laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomization;
- Hospitalized patients with illness of any duration, and at least one of the following:
  - Clinical assessment (evidence of rales/crackles on physical examination) AND SpO2 ≤ 94% on room air, OR
  - Acute respiratory failure requiring supplemental oxygen, high flow oxygen devices, non-invasive ventilation, and/or mechanical ventilation;
- Women of childbearing potential must agree to use contraception for the duration of the study.

Exclusion criteria:

- Refusal to participate expressed by patient or legally authorized representative if they are present;
- Spontaneous blood alanine transferase (ALT)/AST levels > 5 times the upper limit of normal;
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min);
- Pregnancy or breast-feeding;
- Anticipated transfer to another hospital, which is not a study site within 72 hours;
- Patients previously treated with one of the antivirals evaluated in the trial (i.e. remdesivir, interferon ß-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days;
- Contraindication to any study medication including allergy;
- Use of medications that are contraindicated with lopinavir/ritonavir i.e. drugs whose metabolism is highly dependent on the isoform CYP3A with narrow therapeutic range (e.g. amiodarone, colchicine, simvastatine);

- Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram, hydroxyzine, domperidone, pipéraquine;
- Human immunodeficiency virus infection under highly active antiretroviral therapy (HAART);
- History of severe depression or attempted suicide or current suicidal ideation;
- Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula).

Interim analyses

For efficacy and futility, the statistical analysis was performed on the primary outcome measure, and was based on the Haybittle-Peto rule [1,2]. As an add-on trial, DisCoVeRy periodically transferred data to the WHO Solidarity trial (in-hospital mortality, time to hospital discharge, time to mechanical ventilation), whose DSMB examined all Solidarity trial data.

On May 25th 2020, following a safety warning on hydroxychloroquine use [3], enrollment in the hydroxychloroquine arm was suspended at the request of the French Agency of drug Security (Agence Nationale de Sécurité du Médicament). On June 13th, based on the interim analysis of the Solidarity data, the Solidarity and DisCoVeRy trial DSMBs recommended to definitely stop the hydroxychloroquine arm due to futility. This decision was endorsed by the DisCoVeRy steering committee on June 17th. The Solidarity DSMB advised to stop the lopinavir/ritonavir arm due to futility on June, 23th. Thereafter, the DisCoVeRy DSMB further advised to stop both the lopinavir/ritonavir-containing arms due to additional safety concerns on June, 25th. This decision was endorsed by the DisCoVeRy steering committee on June 27th with subsequent interruption on June, 29th.

Statistical analyses

Statistical analyses compared each of the three stopped investigational treatment arms to the control arm. The intention-to-treat population included all randomized participants for whom a valid consent form was obtained. The modified intention-to-treat population included participants from the intention-to-treat population who received at least one dose of the treatment allocated by randomization.

Efficacy analyses were performed on the intention-to-treat population; handling of missing data is described in Supplementary Appendix. Safety analyses were performed on modified intention-to-treat population. Analyses were stratified by baseline severity but not by region of inclusion due to a low number of inclusions in some regions; all tests were two-sided with a type-I error of 0.05, without correction for multiplicity testing.

For the 7-point ordinal scale, data were analyzed using a proportional odds model. Time-to-event data were analyzed using a Cox proportional hazard model. An analysis of covariance was performed for the comparison of oxygenation- and ventilator-free days between groups; 29-day mortality and the number of participants with detectable SARS-CoV-2 in the respiratory tract specimens at each time point were analyzed using a Cochran-Mantel-Haenszel test. Log_{10} normalized SARS-CoV-2 load kinetics was analyzed using a mixed-effects linear model with test of treatment effect on slopes. For safety endpoints, non-prespecified statistical comparisons of the proportions of patients with any i) adverse event, ii) grade 3 or 4 adverse event, or iii) serious adverse event between each investigational treatment arm versus control were performed using the Fisher exact test.

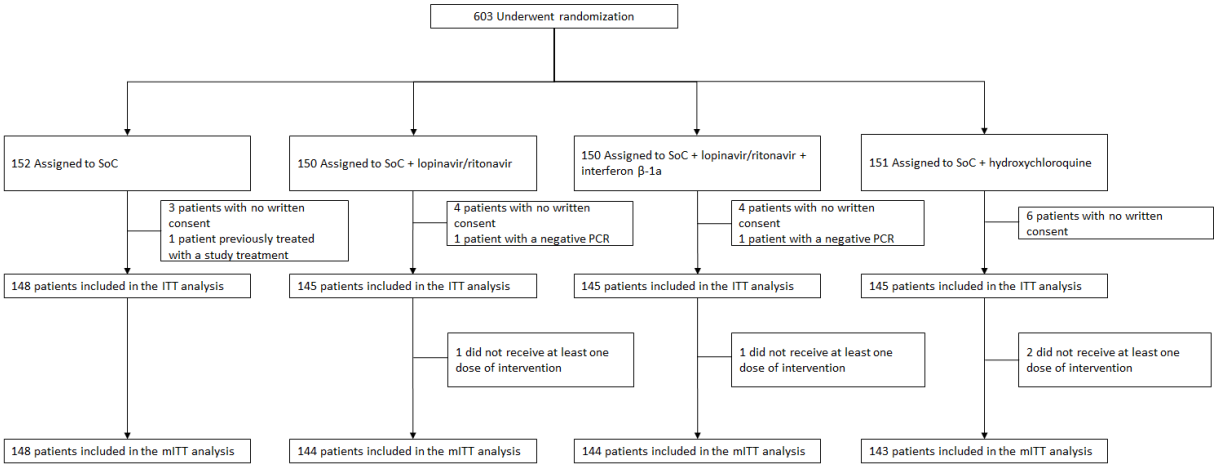
Handling of missing data

For the 7-point ordinal scale, missing data were imputed using the last observation carried forward method, excepted in the case of known death or hospital discharge, in which case the ordinal scale was imputed to the value of 7 (death) or 2 (not hospitalized, limitation of activities), respectively. For NEWS, oxygenation and mechanical ventilation outcomes, missing data were treated using the last observation carried forward method, except in the case of preceding death, in which case patients were imputed to the worst value of the NEWS, or considered to have oxygen or require mechanical ventilation. For time-to-event analyses, patients were censored at day 29, at their date of loss of follow-up, or of study withdrawal, whichever occurred first. As time to event analyses were performed only for positive events (time to an improvement of 2 categories as measured on the 7-point ordinal scale or hospital discharge until day 29, time to National Early Warning Score 2 (NEWS2) ≤2 or hospital discharge until day 29, and time to hospital discharge until day 29), patients who died before the day 29 visit were considered as patients at risk in the survival analysis and censored at day 29. Missing SARS-CoV-2 viral loads were not imputed. For the analysis of viral load by mixed models, undetectable viral load values (i.e. values < 1 log10 copies/10 000 cells) were imputed to half the LoD hence 0.7 log10 copies/10 000 cells. In case of several consecutive undetectable values, only the first one was replaced and the subsequent discarded (until the next detectable value, if values were available afterwards).

Supplementary Figures

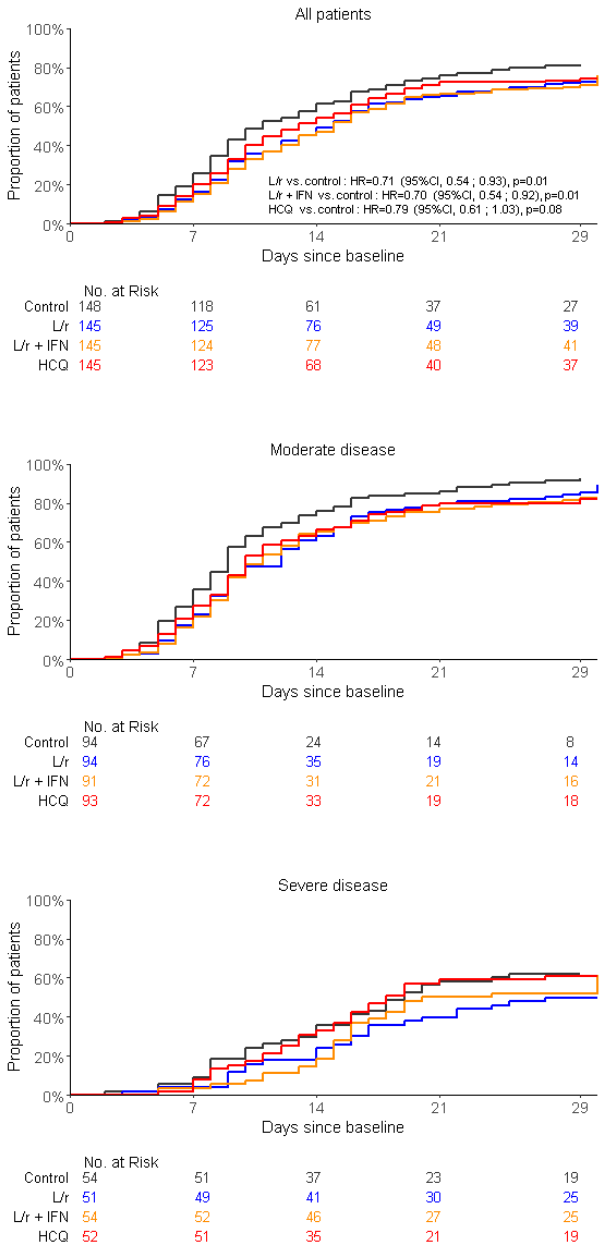
Supplementary Figure S1. Enrollment and randomization of patients in the present analysis of the DisCoVeRy trial.

Patients from all groups received the standard of care, in addition to the treatment allocated by randomization.



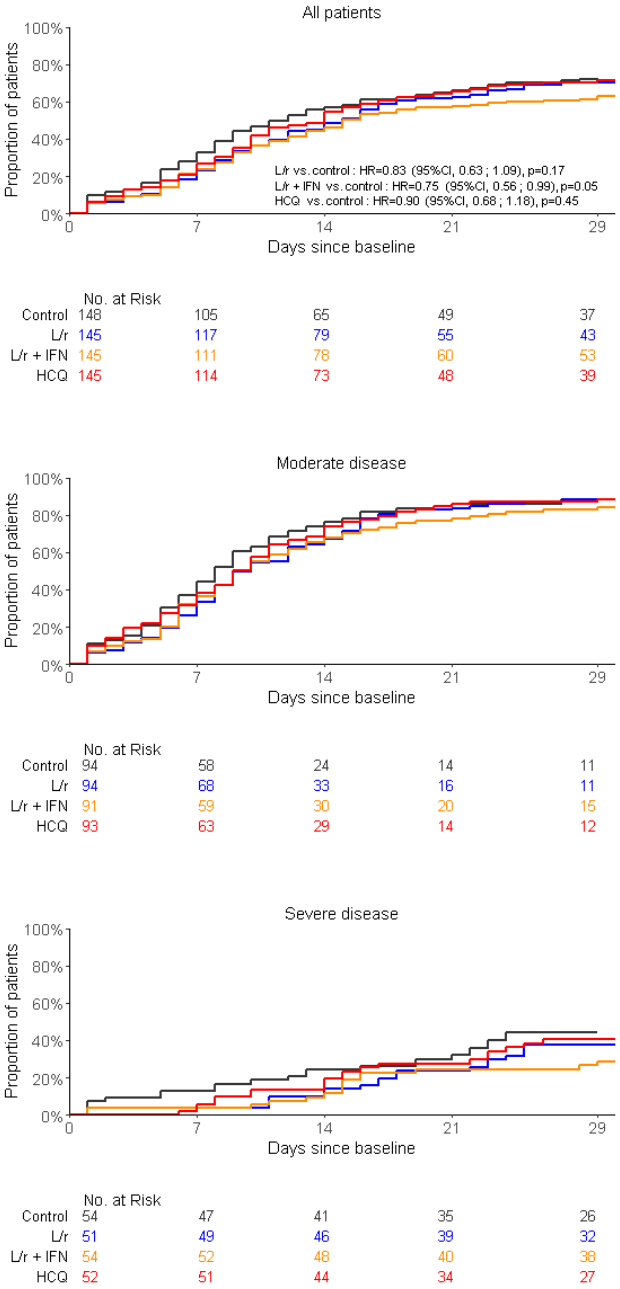
Supplementary Figure S2. Time to improvement of at least 2 categories or the 7-point ordinal scale or hospital discharge between baseline and day 29 in the intention-to-treat population of the DisCoVeRy trial, according to disease severity at baseline in all participants (panel A), in participants with moderate disease at baseline (panel B) and in participants with severe disease at baseline (panel C).

L/r, Lopinavir/ritonavir; L/r + IFN, Lopinavir/ritonavir + interferon ß-1a; HCQ, Hydroxychloroquine; HR, hazard ratio.



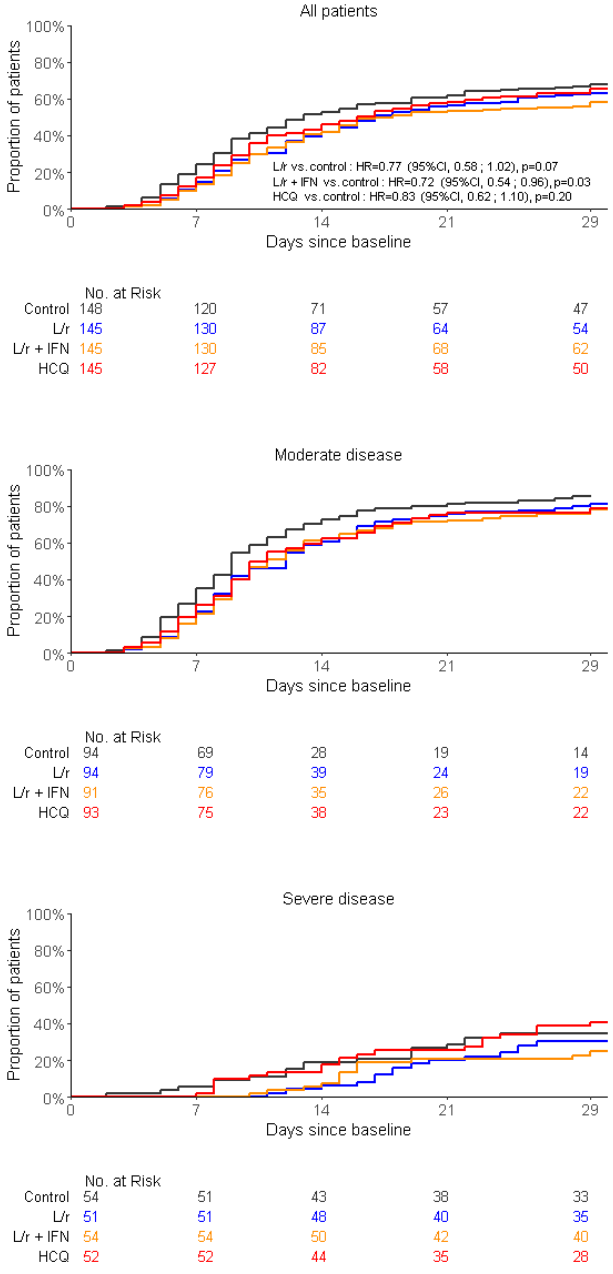
Supplementary Figure S3. Time to National Early Warning Score ≤2 or hospital discharge between baseline and day 29 in the intention-to-treat population of the DisCoVeRy trial, according to disease severity at baseline in all participants (panel A), in participants with moderate disease at baseline (panel B) and in participants with severe disease at baseline (panel C).

L/r, Lopinavir/ritonavir; L/r + IFN, Lopinavir/ritonavir + interferon ß-1a; HCQ, Hydroxychloroquine; HR, hazard ratio.



Supplementary Figure S4. Time to hospital discharge within day 29 between baseline and day 29 in the intention-to-treat population of the DisCoVeRy trial, according to disease severity at baseline in all participants (panel A), in participants with moderate disease at baseline (panel B) and in participants with severe disease at baseline (panel C).

L/r, Lopinavir/ritonavir; L/r + IFN, Lopinavir/ritonavir + interferon ß-1a; HCQ, Hydroxychloroquine; HR, hazard ratio.



Supplementary Tables

Supplementary Table S1. Treatments received during the study course in the patients included in the intention-to-treat population of the DisCoVeRy trial.

Treatment — no. (%)	Overall (N=583)	Control (N=148)	Lopinavir/ritonavir (L/r) (N=145)	Lopinavir/ritonavir + interferon ß-1a (L/r + IFN) (N=145)	Hydroxychloroquine (HCQ) (N=145)
Corticosteroids	172 (29.5%)	41 (27.7%)	41 (28.3%)	47 (32.4%)	43 (29.7%)
- Dexamethasone	42 (7.2%)	7 (4.7%)	9 (6.2%)	14 (9.7%)	12 (8.3%)
- Hydrocortisone	35 (6.0%)	10 (6.8%)	7 (4.8%)	12 (8.3%)	6 (4.1%)
- Methyprednisolone	56 (9.6%)	14 (9.5%)	14 (9.7%)	15 (10.3%)	13 (9.0%)
Interleukin-6 inhibitors	6 (1.0%)	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
- Tocilizumab	6 (1.0%)	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
- Sarilumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Interleukin-1 inhibitors	4 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)	2 (1.4%)
Antibiotics	495 (84.9%)	131 (88.5%)	128 (88.3%)	117 (80.7%)	119 (82.1%)
- Azithromycine	38 (6.5%)	8 (5.4%)	9 (6.2%)	10 (6.9%)	11 (7.6%)
Anticoagulants	549 (94.2%)	138 (93.2%)	136 (93.8%)	137 (94.5%)	138 (95.2%)
Parenteral or enteral nutrition	198 (34.0%)	49 (33.1%)	52 (35.9%)	53 (36.6%)	44 (30.3%)
Vasopressors	218 (37.4%)	53 (35.8%)	54 (37.2%)	61 (42.1%)	50 (34.5%)
Extra-renal replacement/hemofiltration	54 (9.3%)	8 (5.4%)	17 (11.7%)	21 (14.5%)	8 (5.5%)
Neuromuscular blocking agents	194 (33.3%)	47 (31.8%)	43 (29.7%)	58 (40.0%)	46 (31.7%)
Inhaled nitric oxide	41 (7.0%)	8 (5.4%)	8 (5.5%)	16 (11.0%)	9 (6.2%)
Prone positioning	187 (32.1%)	37 (25.0%)	43 (29.7%)	66 (45.5%)	41 (28.3%)

Supplementary Table S2. Proportion of patients with detectable viral loads in the nasopharyngeal swabs at each sampling time, in the intention-to-treat population of the DisCoVeRy trial.

NPS, Nasopharyngeal swab.

	Overall (N=583)		**Control (N=148)**		**Lopinavir/ritonavir (L/r) (N=145)**		**Lopinavir/ritonavir + interferon ß-1a (L/r + IFN) (N=145)**		**Hydroxychloroquine (HCQ) (N=145)**		**L/r vs. control Effect measure (95%CI)**	**L/r + IFN vs. control Effect measure (95%CI)**	**HCQ vs. control Effect measure (95%CI)**
	Moderate (N=372)	**Severe (N=211)**	**Moderate (N=94)**	**Severe (N=54)**	**Moderate (N=94)**	**Severe (N=51)**	**Moderate (N=91)**	**Severe (N=54)**	**Moderate (N=93)**	**Severe (N=52)**			
Detectable viral load in NPS, n/N (%)	144/265 (54.3%)	79/128 (61.7%)	33/66 (50.0%)	24/33 (72.7%)	36/66 (54.5%)	19/30 (63.3%)	39/68 (57.4%)	20/33 (60.6%)	36/65 (55.4%)	16/32 (50.0%)	OR=1.00 (0.57 to 1.78) [P=0.99]	OR=1.04 (0.59 to 1.83) [P=0.89]	OR=0.85 (0.49 to 1.50) [P=0.58]
Detectable viral load in NPS at day 5, n/N (%)	100/245 (40.8%)	57/114 (50.0%)	21/63 (33.3%)	18/31 (58.1%)	23/63 (36.5%)	13/28 (46.4%)	30/60 (50.0%)	15/27 (55.6%)	26/59 (44.1%)	11/28 (39.3%)	OR=0.94 (0.52 to 1.70) [P=0.83]	OR=1.54 (0.85 to 2.78) [P=0.15]	OR=1.05 (0.58 to 1.88) [P=0.88]
Detectable viral load in NPS at day 8, n/N (%)	60/199 (30.2%)	44/122 (36.1%)	17/50 (34.0%)	10/30 (33.3%)	14/50 (28.0%)	7/31 (22.6%)	17/47 (36.2%)	14/34 (41.2%)	12/52 (23.1%)	13/27 (48.1%)	OR=0.69 (0.35 to 1.36) [P=0.28]	OR=1.21 (0.64 to 2.31) [P=0.56]	OR=0.93 (0.48 to 1.79) [P=0.82]
Detectable viral load in NPS at day 11, n/N (%)	23/120 (19.2%)	29/102 (28.4%)	6/29 (20.7%)	6/25 (24.0%)	4/31 (12.9%)	6/25 (24.0%)	4/26 (15.4%)	10/26 (38.5%)	9/34 (26.5%)	7/26 (26.9%)	OR=0.77 (0.30 to 1.96) [P=0.58]	OR=1.26 (0.52 to 3.08) [P=0.61]	OR=1.28 (0.54 to 3.02) [P=0.58]
Detectable viral load in NPS at day 15, n/N (%)	36/263 (13.7%)	23/115 (20.0%)	11/69 (15.9%)	8/32 (25.0%)	7/71 (9.9%)	5/26 (19.2%)	9/60 (15.0%)	2/24 (8.3%)	9/63 (14.3%)	8/33 (24.2%)	OR=0.63 (0.28 to 1.38) [P=0.25]	OR=0.65 (0.29 to 1.46) [P=0.30]	OR=0.91 (0.44 to 1.89) [P=0.81]
Detectable viral load in NPS at day 29, n/N (%)	10/231 (4.3%)	4/88 (4.5%)	3/59 (5.1%)	2/19 (10.5%)	3/63 (4.8%)	1/21 (4.8%)	2/54 (3.7%)	0/23 (0.0%)	2/55 (3.6%)	1/25 (4.0%)	OR=0.73 (0.19 to 2.81) [P=0.65]	OR=0.40 (0.08 to 2.06) [P=0.25]	OR=0.55 (0.13 to 2.38) [P=0.42]

Supplementary Table S3. Number of severe patients with detectable normalized viral load in the lower respiratory tract at each sampling time, in the intention-to-treat population of the DisCoVeRy trial.

	Overall (N=211)	**Control (N=54)**	**Lopinavir/ritonavir (L/r) (N=51)**	**Lopinavir/ritonavir + interferon (L/r + IFN) (N=54)**	**Hydroxychloroquine (HCQ) (N=52)**
Detectable viral load in LRT samples at day 3, n/N (%)	33/35 (94.3%)	9/9 (100.0%)	9/10 (90.0%)	10/11 (90.9%)	5/5 (100.0%)
Detectable viral load in LRT samples at day 5, n/N (%)	36/39 (92.3%)	7/7 (100.0%)	10/10 (100.0%)	11/11 (100.0%)	8/11 (72.7%)
Detectable viral load in LRT samples at day 8, n/N (%)	22/30 (73.3%)	5/7 (71.4%)	7/9 (77.8%)	6/7 (85.7%)	4/7 (57.1%)
Detectable viral load in LRT samples at day 11, n/N (%)	15/26 (57.7%)	5/8 (62.5%)	5/6 (83.3%)	3/7 (42.9%)	2/5 (40.0%)
Detectable viral load in LRT samples at day 15, n/N (%)	1/17 (5.9%)	0/3 (0.0%)	0/5 (0.0%)	1/7 (14.3%)	0/2 (0.0%)
Detectable viral load in LRT samples at day 29, n/N (%)	1/9 (11.1%)	0/2 (0.0%)	0/3 (0.0%)	0/2 (0.0%)	1/2 (50.0%)

Supplementary Table S4. Trough plasma concentrations of lopinavir, ritonavir and hydroxychloroquine at day 1 and day 3 in the intention-to-treat population of the DisCoVeRy trial.

Expected lopinavir concentrations at day 3 were 8100 ng/mL (see ref. 25 in main text).

Data are presented as median (IQR 25-75%).

	Lopinavir/ritonavir arm		**Lopinavir/ritonavir + interferon arm**		**Hydroxychloroquine**
	Lopinavir	**Ritonavir**	**Lopinavir**	**Ritonavir**	
Trough plasma concentration at day 1 (ng/mL)	12 275 (8 342; 17 130) n=87	585 (313; 827) n=72	10 739 (6 777; 14 970) n=71	481 (250; 706) n=59	46 (28; 138) n=61
Trough plasma concentration at day 3 (ng/mL)	20 328 (13 033; 26 640) n=68	536 (312; 1 010) n=58	20 028 (15 290; 25 718) n=73	606 (388; 1 070) n=58	120 (65; 271) n=28

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