Orientações de Acesso a Terapêuticas Experimentais no tratamento de COVID-19 - infeção pelo SARS-CoV-2

Documento elaborado por INFARMED a **13-03-2020** tendo em conta a informação disponível da Agência Europeia do Medicamento, ECDC, OMS e outras fontes

Sumário Executivo

- Não existem atualmente medicamentos autorizados para o tratamento de COVID-19 nem estão também autorizadas quaisquer vacinas;
- Existem, contudo, várias moléculas apontadas como possíveis candidatos terapêuticos:

  O **Remdesivir** é presentemente a molécula promissora no tratamento de COVID-19 tendo em conta o seu largo espetro antiviral (considerando as sequências genéticas do vírus, é expectável que mantenha atividade contra o SARS-CoV-2)[1], a informação *in vitro* e *in vivo* disponível para os coronavírus, assim como a extensiva base de dados de segurança clínica (proveniente de ensaio clínico do vírus Ébola e no contexto do *Monitored Emergency Use of Unregistered and Investigational Interventions* -MEURI) [2] . Adicionalmente, estudos com ratinhos a receber Remdesivir demonstraram uma superioridade de eficácia relativamente à combinação lopinavir/ritonavir + IFN beta. Há dados preliminares já publicados na *Nature Communications* que são favoráveis a uso de Remdesivir neste contexto. [3]

  Estão em recrutamento ativo dois ensaios clínicos com Remdesivir na China, em Hubei e em Beijing, respetivamente em doentes hospitalizados com doença ligeira a moderada (finalização estimada para 27 abril 2020) e outro em doentes com doença grave (finalização estimada para 1 maio 2020). Encontram-se em curso, três ensaios clínicos nos EUA (No Nebraska; por iniciativa do NIH em fase de recrutamento; finalização estimada para abril 2023 e dois outros ainda a aguardar a abertura de centros de ensaio). Na Europa estão previstos dois ensaios clínicos promovidos pela Gilead e um pelo INSERM.[4, 5, 6]

  A associação **lopinavir/ritonavir** é outra das opções. Trata-se do medicamento antirretroviral já autorizado na União Europeia (EU), que pertence ao grupo dos inibidores da protease, utilizado em monoterapia ou em associação com o IFN beta 1b, combinação esta que está a ser estudada num ensaio clínico no âmbito do tratamento da Síndroma Respiratória do Médio Oriente por coronavírus (MERS) - ensaio MIRACLE. Existem dúvidas sobre se a combinação exerce atividade em humanos nas doses testadas (as mesmas utilizadas no HIV).[7]

  A cloroquina e hidroxicloroquina têm apresentado resultados promissores em termos de EC_{50} em células Vero. No entanto, permanece por esclarecer se se traduz em eficácia no Homem em COVID-19. [8,9]

  Estas são as potenciais opções terapêuticas de maior relevância, estando ainda a ser estudadas outras opções como Favipiravir, Oseltamivir, Umifenovir, Darunavir + Cobicistat, Azivudine,

[1] Brown et al (2019) *Antiviral Research*, 169, 104541. https://doi.org/10.1016/j.antiviral.2019.104541
[2] WHO - Notes for the record: Consultation on Monitored Emergency Use of. Unregistered and Investigational Interventions (MEURI) for. Ebola Virus Disease (EVD); https://www.who.int/ebola/drc-2018/notes-for-the-record-meuri-ebola.pdf
[3] Sheahan et al (2020). *Nature communications*, 11(1), 222. https://doi.org/10.1038/s41467-019-13940-6
[4] Severe 2019-nCoV Remdesivir RCT (NCT04257656); https://clinicaltrials.gov/ct2/show/NCT04257656?intr=Remdesivir&draw=2&rank=1
COVID-19 : 20 projets de recherche sélectionnés pour lutter contre l'épidémie; https://presse.inserm.fr/covid-19-20-projets-de-recherche-selectionnes-pour-lutter-contre-l-epidemie/38640/
[5] Mild/Moderate 2019-nCoV Remdesivir RCT (NCT04252664); https://clinicaltrials.gov/ct2/show/record/NCT04252664?term=remdesivir&draw=2
[6] COVID-19 : 20 projets de recherche sélectionnés pour lutter contre l'épidémie; https://presse.inserm.fr/covid-19-20-projets-de-recherche-selectionnes-pour-lutter-contre-l-epidemie/38640/
[7] Arabi et al. (2020) *Trials*, 21, 8; https://doi.org/10.1186/s13063-019-3846-x
[8] Wang et al (2020) *Cell Research* 30, 269–271 (2020); https://doi.org/10.1038/s41422-020-0282-0
[9] Yao et al (2020) *Clinical Infectious Diseases* Mar 9. pii: ciaa237 (2020); https://doi.org/10.1093/cid/ciaa237.

Triazavirin, células estaminais, glucocorticoides, imunoglobulinas, anticorpos monoclonais e policlonais, plasma dos convalescentes, entre outros.[10]

- Limitações dos níveis de evidência actuais: Conhecimentos insuficientes da evolução clínica de COVID-19, informações epidemiológicas insuficientes para orientar com precisão a definição da população-alvo e *endpoints* finais de eficácia, atividade in vitro / in vivo contra SARS-CoV-2, dados insuficientes sobre a dosagem apropriada de terapêutica a ser usada em COVID-19, dados limitados sobre eficácia e segurança da terapêutica candidata disponível contra SARS-nCoV-2.
- No que respeita às vacinas, não existem também presentemente vacinas aprovadas para o SARS-CoV-2 ou para outros coronavírus. A OMS convocou um grupo de peritos para analisar a priorização de possíveis candidatos para o desenvolvimento de vacinas. Existem informações sobre vacinas que interessaria ponderar a sua citação[11,12]
- Este documento pretende informar sobre as potenciais terapêuticas experimentais ou vacinas para a doença pelo novo Coronavirus 2019- SARS-CoV-2 e o potencial acesso aos mesmos **alertando para o acesso muito limitado à data a estas opções**.

O INFARMED, I.P., irá atualizando este documento à medida que surjam novas informações sobre potenciais terapêuticas e vacinas para utilização em COVID-19.

[10] Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

[11] Boodman E. Researchers rush to test coronavirus vaccine in people without knowing how well it works in animals. STATNEWS; https://www.statnews.com/2020/03/11/researchers-rush-to-start-moderna-coronavirus-vaccine-trial-without-usual-animal-testing/

[12] Lee J. These nine companies are working on coronavirus treatments or vaccines — here's where things stand. MarketWatch; https://www.marketwatch.com/story/these-nine-companies-are-working-on-coronavirus-treatments-or-vaccines-heres-where-things-stand-2020-03-06

Medicamentos potencialmente utilizáveis na doença por coronavírus SARS-CoV-2 e vacinas

1 – Iniciativas da OMS

A OMS, no âmbito do plano estratégico global *R&D Blueprint*[13], que tem como objetivo a rápida iniciação de atividades de R&D durante cenários epidémicos, convocou um grupo de peritos para analisar a priorização de possíveis medicamentos como candidatos terapêuticos para o tratamento da infeção pelo novo coronavírus SARS-CoV-2.

De forma a estabelecer o desenho e realização de ensaios clínicos em regiões afetadas pelo SARS-CoV-2, é muito importante que se estabeleça a **priorização das moléculas mais adequadas** e que neste sentido seja avaliada a evidência disponível em termos de segurança e eficácia, destas moléculas candidatas.

Mais informação encontra-se disponível em:

https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1

No que respeita às **vacinas,** a OMS convocou também um grupo de peritos a fim de constituir um grupo de trabalho para avaliar priorização de candidatos em termos de vacinas para COVID-19, assumindo a necessidade de acelerar o respetivo desenvolvimento. Este grupo tem como objetivo rever as vacinas candidatas para COVID-19 e também as vacinas candidatas a outros coronavírus e discutir o seu eventual valor na proteção contra o SARS-CoV-2[14]. Nas recomendações emitidas pelo grupo ficou estipulado dar prioridade às vacinas candidatas para o novo coronavírus, dado que a análise concluiu que as vacinas para MERS e SARS não poderão ser utilizadas. É esperado que sejam reconstruídas novas vacinas que incluam antigénios do SARS-CoV-2. No entanto a informação disponível sobre estas vacinas é muito preliminar. Há vários tipos de opções para o desenvolvimento de vacinas com base em diversas plataformas como sejam ácidos nucleicos (mRNA e DNA), vacinas com vetores virais, e com subunidades proteicas. Será dada prioridade em termos de preferência, a uma resposta imunitária apenas com uma dose única de vacina, mas as vacinas candidatas que requeiram 2 doses, serão ainda assim consideradas.

Mais informação disponível em:https://www.who.int/blueprint/priority-diseases/key-action/prioritization-candidate-vaccines-ncov2019.pdf?ua=1

2 – Iniciativas da Agência Europeia de Medicamentos (EMA)

Segundo informação publicada pela EMA no passado dia 4 de fevereiro, e no âmbito dos recentes acontecimentos e para contribuir para uma resposta global ao surto de COVID-19, a EMA está a tomar medidas concretas para acelerar o desenvolvimento e a disponibilização de medicamentos para o tratamento e prevenção do novo coronavírus, tendo ativado o *Plan for managing emerging*

[13] WHO R&D Blueprint – Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection. 24 January 2020; https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1

[14] WHO R&D Blueprint novel Coronavirus (nCov) - Vaccine prioritization for clinical trials. 30 January 2020;https://www.who.int/blueprint/priority-diseases/key-action/prioritization-candidate-vaccines-ncov2019.pdf?ua=1

health threats[15]. A EMA está a analisar o cenário em termos de eventuais possibilidades de potenciais antivirais ou vacinas para tratar ou prevenir as infeções pelo novo coronavírus. A EMA está também a analisar a informação disponível em termos de *pipelines* de desenvolvimento de medicamentos, estando em condições de colaborar através da sua rede de peritos, para conceder aconselhamento científico e dar *feedback* imediato no desenvolvimento de novas opções terapêuticas, fazendo uso de todas as suas ferramentas regulamentares. A EMA está a colaborar com outros organismos europeus como a Comissão Europeia (CE), *Health Security Committee*, *European Centre for Disease prevention and control* (ECDC) e a OMS, bem como outras autoridades reguladoras internacionais, como a *International Coalition of Regulatory Authorities* (ICMRA).[16]

3 – Atuação do INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

O INFARMED, I. P., encontra-se a acompanhar a nível nacional e a nível Europeu no contexto da Agência Europeia de Medicamentos os assuntos relacionados com o novo coronavírus.

De acordo com a Deliberação n.º 1546/2015 do Infarmed, a comercialização e a utilização em Portugal de medicamentos não possuidores de autorização de introdução no mercado depende de autorização a conceder nos termos do regulamento sobre autorização de utilização excecional (AUE).

Cada pedido de AUE apresentado ao INFARMED, I.P. é analisado e avaliado individual e casuisticamente, tendo em conta as características dos doentes, quadros clínicos particulares e a utilização do medicamento nesse contexto.

Informação sobre os ensaios clínicos em curso ou planeados para diversas opções terapêuticas para o tratamento de COVID-19

Remdesivir (Gilead Sciences, Inc.)

(fonte: Site da agência Dinamarquesa - Versão 10.03.2020 10:00)[17]

Produto; descrição; TAIM	ID estudo	Local estudo	Desenho estudo	Outcome primário	Estado ensaio	Importância
Remdesivir/GS-5734 Nucleoside Inhibitor Not licensed	https://clinicaltrials.gov/ct2/show/NCT04252664?cond=COVID-19&draw=2&rank=1 NCT04252664	China, Hubei	A Phase 3 Randomised, Double-blind, Placebo-controlled Multicenter Study N=308 hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease randomised to	Time to Clinical Recovery defined as the time (in hours) from initiation of study treatment (active or placebo) until	Recruiting; Estimated study completion: April 27, 2020	High

[15] EMA plan for emerging health threats. EMA/863454/2018. 10 December 2018; https://www.ema.europa.eu/en/documents/other/ema-plan-emerging-health-threats_en.pdf

[16] European Medicines Agency - Addressing the potential impact of novel coronavirus disease (COVID-19) on medicines supply in the EU. 10 March 2020; https://www.ema.europa.eu/en/news/addressing-potential-impact-novel-coronavirus-disease-covid-19-medicines-supply-eu

[17] Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

			Remdesivir, or placebo	normalisation of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours.		
GS-5734/ Remdesivir	https://clinicaltrials.gov/ct2/show/NCT04257656?term=remdesivir&draw=2&rank=1 NCT04257656	China, Beijing	A Phase 3 Randomised, Double-blind, Placebo-controlled, Multicenter Study N= 453 Hospitalized Adult Patients With Severe 2019-nCoVRespiratory Disease ranomised to Remdesivir, or placebo	Time to Clinical Improvement (TTCI), two steps in a Six-category ordinal scale:1 (discharged) to 6 (death), censoring at day 28	Recruiting; Estimated study completion: May 1, 2020	High
GS-5734/ Remdesivir	https://clinicaltrials.gov/ct2/show/NCT04280705?term=remdesivir&draw=2&rank=3 NCT04280705:	Nebraska, US	Phase 2 A Multicenter, Adaptive, Randomised Blinded Controlled Trial N=394 Hospitalized Adults randomised to remdesivir, or placebo	Percentage of subjects reporting each severity rating on the 7-point ordinal scale (death – not hospitalized)	Recruiting; Estimated study completion: April 2023	High
GS-5734/ Remdesivir	https://clinicaltrials.gov/ct2/show/NCT04292730 NCT04292730	???	Phase 3 open label randomised controlled trial. N=600 with moderate covid-19 randomised 1:1:1 to remdesivir 100 mg for 5 days, remdesivir 100 mg for 10 days, or standard of care	Proportion of participants in each group discharged by day 14	Not yet recruiting, Estimated study completion May 2020	High
GS-5734/ Remdesivir	https://clinicaltrials.gov/ct2/show/NCT04292899 NCT04292899	???	Phase 3 open label randomised controlled trial. N=400 with severe covid-19 randomised to 100 mg for 5 days or 100 mg for 10 days.	Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14	Not yet recruiting, Estimated study completion May 2020	High

Critérios de elegibilidade e exclusão dos EC em curso (fonte: clinical.trials.gov[18])

Elegibility	**Moderada**	**Grave**
Key Inclusion Criteria	18 Years and older (Adult, Older Adult)	18 Years and older (Adult, Older Adult)
	Willing and able to provide written informed consent prior to performing study procedures	Willing and able to provide written informed consent prior to performing study procedures
	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization
	Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal	Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal
Key Inclusion Criteria:	Peripheral capillary oxygen saturation (SpO2) > 94% on room air at screening	Peripheral capillary oxygen saturation (SpO2) ≤ 94% on room air at screening
	Radiographic evidence of pulmonary infiltrates	Radiographic evidence of pulmonary infiltrates
Key Exclusion Criteria	Requiring mechanical ventilation at screening	Requiring mechanical ventilation at screening
	Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN)	Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN)
	Creatinine clearance < 50 mL/min	Creatinine clearance < 50 mL/min
		Evidence of multiorgan failure

[18] https://clinicaltrials.gov/ct2/results?cond=covid&term=&cntry=&state=&city=&dist=

Lopinavir + Ritonavir (AbbVie Deutschland GmbH & Co. KG e medicamentos genéricos)

(fonte: Site da agência Dinamarquesa - Versão 10.03.2020 10:00)[19]

Produto; descrição; TAIM	ID estudo	Local estudo	Desenho estudo	Outcome primário	Estado ensaio	Importância
Ritonavir + Lopinavir (Protease inhibitors HIV infection)	https://clinicaltrials.gov/ct2/show/NCT04255017?draw=2 NCT04255017	Tongji Hospital, China	Phase 4 single blinded, Prospective, Randomised Controlled Cohort Study to Compare the Efficacy of Three Antiviral Drugs (Abidol Hydrochloride (Umifenovir), Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia. N=400 patients with CT manifestation of viral pneumonia + mCoV positive randomised to Abidol hydrochloride, Oseltamivir, or Lopinavir/ritonavir	Rate of disease remission (Time Frame: two weeks) Time for lung recovery (Time Frame: two weeks)	Not Recruiting; Estimated study completion: July 1, 2020	High
Ritonavir + Lopinavir (Kaletra)	http://www.chictr.org.cn/showprojen.aspx?proj=48824 ChiMCTR2000002940	Wuhan, China	N=60 randomised to traditional Chinese medicine, Lopinavir/ritonavir, or traditional Chinese medicine + lopinavir/ritonavir	The rate of remission	Not Recruiting; Estimated study completion: Dec 31, 2020	Low
Ritonavir + Lopinavir (Kaletra)	NCT04252885	China, Guangdong	Open label, 125 patients Randomised 2:2:1 to Lopinavir /Ritonavir Tablets, Arbidol, or ordinary treatment	The rate of virus inhibition	Recruiting; Estimated study completion: July 31, 2020	Medium
Ritonavir + Lopinavir (Kaletra)	NCT04276688	Hong Kong	Phase 2 study Open-label randomised controlled trial among adult patients hospitalized and	Time to negative nasopharyngeal swab (NPS) 2019-n-	Recruiting; Estimated study completion: July 31, 2022	Low

[19]Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

			confirmed covid-19 infection N=70 hospitalised patients with confirmed covid 19 infection randomised to Lopinavir/ritonavir, Ribavirin, or Interferon Beta-1B	CoV coronavirus viral RT-PCR		
Ritonavir + Lopinavir (Kaletra)	NCT04261907 ChiCTR2000029603 http://www.chictr.org.cn/showproj.aspx?proj=49075	Zhejiang University	Randomised, Open-label, Multi-centre Clinical Trial N=160 patients with pneumonia caused by covid-19 randomised to ASC09/ritonavir or lopinavir/ritonavir	The incidence of composite adverse outcome (time frame 14 days)	Recruiting (according to Chinese website that was updated) Estimated study completion: June 30, 2020	Medium
Ritonavir + Lopinavir (Kaletra)	NCT04291729	China, Jiangxi	50 patients with covid 19 randomised 1:1:1:1:1 to Ganovo+ritonavir with or without interferon atomization; Pegasys; Novaferon atomization; Lopinavir+ritonavir; Chinese medicines +interferon atomization	Rate of composite adverse outcomes (Time frame: 14 days)	Recruiting; Estimated study completion: April 30, 2020	Low
Ritonavir + Lopinavir+ interferon +/- ribavirin	ChiCTR2000029387 http://www.chictr.org.cn/showproj.aspx?proj=48782	Chongqing, Chin	N= 108 patients with mild or moderate covid-19 randomised to Ribavirin + Interferon alpha-1b, lopinavir / ritonavir + interferon alpha-1b, or Ribavirin + LPV/r+Interferon alpha-1b;	The time to 2019-nCoV RNA negativity in patients;	Recruiting Study execute time: From 2020-01-25 to 2021-01-25	Low
Ritonavir + Lopinavir	ChiCTR2000029539 http://www.chictr.org.cn/showproj.aspx?proj=48991	Tongji, Hubei, China	Open label study. N=328 Patients with mild covid-19 or unexplained viral pneumonia randomised 1:1 to conventional standardized treatment + Lopinavir/Ritonavir, or conventional standardized treatment	The incidence of adverse outcome within 14 days after admission : Patients with conscious dyspnea, SpO2 = 94% or respiratory frequency	Recruiting; From2020-02-03 To 2021-02-02	Medium

				= 24 times / min in the state of resting without oxygen inhalation;		
Lopinavir/Ritonavir	ChiCTR2000030187 http://www.chictr.org.cn/showproj.aspx?proj=50057	Hubei, China	N=60 randomised to lopinavir/ritonavir, or Routine symptomatic support treatment	Endotracheal intubation rate, time frame: 14 days Mortality, time frame: 14 days	Not yet recruiting; From2020-02-25 To 2020 -03-10	Low
Lopinavir / Ritonavir (Kaletra) vs Abidol vs ASC09/ Ritonavir (ASC09F)	ChiCTR2000029759 http://www.chictr.org.cn/showproj.aspx?proj=49352	Chongqing	A multicenter, randomised, open label, controlled trial 60 patients randomised to Lopinavir / Ritonavir (Kaletra) + IFN aerosol inhalation, Abidol and IFN aerosol inhalation, or ASC09/ Ritonavir (ASC09F) and IFN aerosol inhalation	Time to recovery.	From2020-02-15 To 2020-05-01	Low
Carrimycin vs Ritonavir + Lopinavir; Carrimycin licenced in China	https://clinicaltrials.gov/ct2/show/NCT04286503 NCT04286503 http://www.chictr.org.cn/showprojen.aspx?proj=49514 ChiCTR2000029867	Beijing YouAn Hospital and other hospitals in China	A Multicenter, Randomised, Open-controlled Study, N=520 patients stratified by severity, Randomised to carrimycin or lopinavir/ritonavir	Fever to normal time (day) (Time Frame: 30 days) Pulmonary inflammation resolution time (HRCT) (day) (Time Frame: 30 days) Negative conversion (%) of 2019-nCOVRNA in gargle (throat swabs) at the end of treatment (Time Frame: 30 days	Not yet recruiting; Estimated study completion, Feb 28, 2021	Medium
Lopinavir/ritonavir+ interferon-a2b	ChiCTR2000029308	Wuhan, China	A randomised, open-label, blank-controlled trial;	Clinical improvement time of 28 days	Recruiting; Study execute	Medium

	http://www.chictr.org.cn/showproj.aspx?proj=48684		N=160 randomised 1:1 to Lopinavir-ritonavir + interferon-a2b, or Conventional standardized treatment;	after randomization on a 7-point scale	time From 2020-01-10 to 2021-01-10	
Lopinavir/ritonavir + emtritabine /Tenofovir alafenamide fumarate	ChiCTR2000029468 http://www.chictr.org.cn/showproj.aspx?proj=48919	Sichuan, China	Single arm study with historical controls Patients with covid-19 N=60 in the intervention arm N=60 historical controls	Patient survival rate	Not yet recruiting From 2020-02-01 To 2020-06-30	Low

Favipiravir

(ou T-705 ou Avigan; Antiviral experimental; derivado Pirazinecarboxamida inibidor da RNA polimerase viral; autorizado para influenza no Japan)

(fonte: Site da agência Dinamarquesa - Versão 10.03.2020 10:00)[20]

Produto; descrição; TAIM	**ID estudo**	**Local estudo**	**Desenho estudo**	**Outcome primário**	**Estado ensaio**	**Importância**
Favipiravir (or T-705 or Avigan)	http://www.chictr.org.cn/showprojen.aspx?proj=49015 ChiCTR2000029548	Zhejiang, China	N=30, Randomised 1:1:1 to BaloxavirMarboxil, Favipiravir, or Lopinavir-Ritonavir;	Primary outcome: time to negative PCR and time to clinical improvement	Not recruiting; Estimated study completion: June 2020	Medium
Favipiravir (or T-705 or Avigan)	http://www.chictr.org.cn/showprojen.aspx?proj=49013 ChiCTR2000029544	Zhejiang, China	N= 30 with Coronavirus pneumonia Randomised 1:1:1 to antiviral treatment + Baloxavir, antiviral treatment + Marboxil, or antiviral treatment	Primary outcome: time to negative PCR Time to clinical improvement	Not recruiting; Estimated study completion: June 2020	Low
Favipiravir (or T-705 or Avigan)	http://www.chictr.org.cn/showproj.aspx?proj=49042 ChiCTR2000029600	Guangdong, China	N=90 with corona pneumonia Randomised 1:1:1 to alpha-Interferon, Lopinavir and Ritonavir + alpha-Interferon, or Favipiravir +	5 primary outcomes - not concrete: Declining speed of Novel Coronavirus by PCR; Negative Time of Novel	Recruiting; Estimated study completion: May 2020	Low

[20] Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

			alpha-Interferon atomization	Coronavirus by PCR; Incidence rate of chest imaging; Incidence rate of liver enzymes; Incidence rate of kidney damage		
Favipiravir (or T-705 or Avigan)	http://www.chictr.org.cn/showprojen.aspx?proj=49988 ChiCTR2000030113	Guangdong, China	N=30 with corona pneumonia with poorly responsive ritonavir Randomised to ritonavir or favipiravir	Blood routine tests, Liver function examination, Renal function examination, Blood gas analysis, Chest CT examination	Recruiting; Estimated study completion: May 31, 2020	Low
Fapilavir Approved by China for covid-19 treatment by February 17, 2020.	ChiCTR2000029996 http://www.chictr.org.cn/showproj.aspx?proj=49510	Beijing, China	Randomised, open label, controlled trial. N=60 patients with covid-19 of ordinary type randomised to low, middle or high dose fapilavir for 10 days	Time to Clinical Recovery defined as normal body temperature and cough relief	Recruiting	Low
Favipiravir + bromhexine	NCT04273763 https://clinicaltrials.gov/ct2/show/NCT04273763	China, Zhejiang	Open label N=60 with mild corona pneumonia randmised 1:1 to favipiravir + interferon-alfa + arbidol hydroglhoride + interferon alfa2b, or arbidol hydroglhoride + interferon alfa2b	Time to clinical recovery after treatment	Enrolling by Invitation Estimated study completion: April 30, 2020	Low

Cloroquina / Hidroxicloroquina

Foi recentemente publicado um estudo pela *Nature*, a 4 de fevereiro de 2020, que atribui à **cloroquina** uma eventual possibilidade de ser considerada no âmbito dos estudos de possíveis candidatos à terapêutica da COVID-19. Tal facto baseia-se nos resultados descritos neste estudo, em que foi avaliada a eficácia *in vitro* de 5 antivirais, incluindo a ribavirina, a nitazoxanida, nafamostat, cloroquina, remdesivir e favipiravir, contra um isolado clínico de SARS-CoV-2. O estudo

concluiu que o remdesivir e a **cloroquina,** possuem capacidade para inibir *in vitro* o novo coronavírus SARS-CoV-2.[21] A **cloroquina** pertence ao grupo dos medicamentos antimaláricos, amplamente utilizado, e recentemente categorizado como um fármaco antiviral com potencial espetro de ação alargado. Para além da sua atividade antiviral, a cloroquina possui uma atividade imunomoduladora, que pode, através de um efeito sinergético aumentar o seu efeito antiviral *in vivo*. Uma publicação chinesa reforça também a eficácia desta molécula[22], no entanto permanecem algumas dúvidas, tendo em conta estudos clínicos anteriores em Chykungunyan [23] influenza e dengue. A utilização da cloroquina e a atividade contra o SARS-CoV-2 encontra-se em discussão.

A **hidroxicloroquina** foi reportada (Xueting et al, 2020) *in vitro* como sendo três vezes mais potente do que o fosfato de cloroquina na inibição do SARS-CoV-2. A hidroxicloroquina partilha o mesmo mecanismo de ação que o da cloroquina, mas o seu perfil de segurança é mais tolerável fazendo dela o fármaco preferido para tratar malária e condições autoimunes. Os autores propõem, que o efeito imunomodulador da hidroxicloroquina pode também ser útil no controlo da tempestade de citocinas que ocorre na fase final em doentes infetados pelo SARS-CoV-2. Contudo, não há atualmente evidências clínicas que apoiem o uso de hidroxicloroquina na infeção por SARS-CoV-2. [24]

Lista atualizada dos Ensaios Clínicos em curso ou planeados com Cloroquina/Hidroxicloroquina

(fonte: Site da agência Dinamarquesa - Versão 10.03.2020 10:00) [25]

Produto; descrição; TAIM	ID estudo	Local estudo	Desenho estudo	Outcome primário	Estado ensaio	Importância
Chloroquine	NCT04261517 https://clinicaltrials.gov/ct2/show/NCT04261517	China, Shanghai	Phase 3, randomiased, open label N=30 with mild and severe covid19 randomised to hydroxychloroquine or conventional treatment	Virological clearance rate at day 3, 5, or 7 and the mortality rate at weeks 2	Not yet recruiting; Estimated primary completion date/ Estimated study completion: August 31, 2020/December 31, 2020	Low
Chloroquine	ChiCTR2000029542 http://www.chictr.org.cn/showproj.aspx?proj=48968	Guangdong, China	Phase 4, open label, non-randomised N=20 with covid-19 Treatment: chloroquine or conventional treatment	Viral negative-transforming time, 30-day cause specific mortality	Recruiting From2020-02-03 To 2020-07-30	Low
Chloroquine	ChiCTR2000029559	Hubei, China	Double blind	The time when the	Recruiting;	High

[21] Wang, M., Cao, R., Zhang, L. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 30, 269–271 (2020); https://doi.org/10.1038/s41422-020-0282-0
[22] Gao J, Tian Z, Yang X. *Bioscience Trends*. (2020) Feb 19. https://doi.org/10.5582/bst.2020.01047
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[24] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases Mar 9. pii: ciaa237 (2020); https://doi.org/10.1093/cid/ciaa237
[25] Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

	http://www.chictr.org.cn/showproj.aspx?proj=48880		N=300 with Covid-19 randomised 1:1:1 to Hydroxychloroquine 0.1 oral 2/ day, Hydroxychloroquine 0.2 oral 2/ day, or placebo	nucleic acid of the novel coronavirus turns negative T cell recovery time	From2020-01-31 To 2020-02-29	
Chloroquine vs liponavir/ritonavir	ChiCTR2000029609 http://www.chictr.org.cn/showproj.aspx?proj=49145	Guangdong, China	A prospective, open-label, multiple-center study or patients with Covid-19 stratified by severity. Mild symptoms randomised to chloroquine phosphate (n=59) lopinavir/ritonavir (59), or Chloroquine + lopinavir/ritonavir (59) Severe symptoms randomised to Chloroquine phosphate (n=14) or lopinavir/ritonavir (n=14)	Primary Outcome(s) virus nucleic acid negative-transforming time;	From2020-02-10 To 2020-12-31	Low
Chloroquine and lopinavir/ritonavir	ChiCTR2000029741 http://www.chictr.org.cn/showproj.aspx?proj=49263	Guangdong, China	Open label study N=112 cases with Confirmed Covid-19 randomised to Chloroquine, or Lipinavir/ritonavir	Several primary outcomes are stated: length of stay, mortality and other	Recruiting; From2020-02-12 To 2020-12-31	Low
Chloroquine	ChiCTR2000029740 http://www.chictr.org.cn/showproj.aspx?proj=49317	Tongji hospital, Hubei, China	Open label COVID-19 Randomised to hydroxychloroquine 0.2 mg bid (n=52), or conventional therapy (n=24)	Oxygen index, respiratory rate, lung radiography, lymphocyte count at sees 1,2,3,and 4.	Recruiting From2020-02-11 To 2020-02-29	Low
Chloroquine	ChiCTR2000029762 http://www.chictr.org.cn/showproj.aspx?proj=49404	Chongqing, China	60 patients with severe covid-19	Negative conversion rate of COVID-19 nucleic acid Lung inflammation absorption ratio	Cancelled due to lack of patients	Low

Chloroquine	ChiCTR2000029761 http://www.chictr.org.cn/showproj.aspx?proj=49400	Chongqing, China	240 patients randomised to 3 different doses of hydroxychloroquine or conventional treatment	Negative conversion rate of 2019-nCoV nucleic acid Lung inflammation absorption ratio	Cancelled due to lack of patients	Low
Chloroquine	ChiCTR2000029826 http://www.chictr.org.cn/showproj.aspx?proj=49481	Hubei, China	Randomised double blinded trial. Serious or critically ill patients randomised to chloroquine (n=30) or placebo (n=15)	Mortality rate	Not yet recruiting. From2020-02-17 To 2020-03-17	Medium
Chloroquine	ChiCTR2000029868 http://www.chictr.org.cn/showproj.aspx?proj=49524	Hubei, China	a multicenter, randomised controlled trial N=200 with mild covid-19 randomised to hydroxychloroquine or conventional treatment	Viral nucleic acid test	Recruiting; From2020-02-06 To 2020-07-31	Low
Chloroquine	ChiCTR2000029837 http://www.chictr.org.cn/showproj.aspx?proj=49495	Hubei, China	A randomised, double-blind, parallel, controlled trial Mild or moderate covid19 Randomised to hydroxychloroquine (n=80) or Placebo (n=40)	Time of conversion to be negative of novel coronavirus nucleic acid	Not yet recruiting; From2020-02-17 To 2020-03-17	Medium
Chloroquine	ChiCTR2000029939 http://www.chictr.org.cn/showproj.aspx?proj=49612	Zhejiang, China	Single-blind, Randomised, Controlled Clinical Trial N=100 patients with covid-19 (severity unknown), randomised to chloroquine phosphate or placebo	Length of hospital stay	Recruiting; From2020-02-06 To 2021-02-06	Low
Chloroquine	ChiCTR2000029935 http://www.chictr.org.cn/showproj.aspx?proj=49607	Zhejiang, China	Single arm study, N=100 patients with covid-19 (severity unknown), treated with chloroquine phosphate	Length of hospital stay	Recruiting ; From2020-02-06 To 2021-02-06	Low
Hydroxychloroquine sulfate vs phosphate chloroquine	ChiCTR2000029899 http://www.chictr.org.cn/sho	Hubei, China	Randomised, Open-label, Parallel, Controlled Trial	Time to clinical recovery (time	Recruiting; From2020-02-17 To 2020-04-30	Low

	wproj.aspx?proj=49536		N=100 with mild or moderate covid-19 randomised to Hydroxychloroquine sulfate, or phosphate chloroquine	frame 28 days)		
phosphate chloroquine	ChiCTR2000029898 http://www.chictr.org.cn/showproj.aspx?proj=49482	Hubei, China	Randomised, Open-label, Parallel, Controlled Trial N=100 with severe covid-19 randomised to Hydroxychloroquine sulfate, or phosphate chloroquine	Time to clinical improvement (time frame 28 days)	Recruiting; From2020-02-17 To 2020-04-30	Low
Hydroxychloroquine sulfate vs phosphate chloroquine	ChiCTR2000029992 http://www.chictr.org.cn/showproj.aspx?proj=49574	Hubei, China	Randomised, Open-label, Parallel, Controlled Trial N=100 with severe covid-19 randomised to Hydroxychloroquine sulfate (n=40), or phosphate chloroquine (n=40), or routine treatment (n=20)	Clinical recovery time (6-point scale); Changes in viral load of upper and lower respiratory tract	Not yet recruiting; From2020-02-17 To 2020-05-20	Low
Chloroquine phosphate	ChiCTR2000029988 http://www.chictr.org.cn/showproj.aspx?proj=49218	Hubei, China	Open label clinical trial. N=80 patients with severe covid-19 randomised to chloroquine phosphate or no treatment	Time to clinical recovery	Recruiting; From2020-02-13 To 2020-05-31	Low
Chloroquine phosphate aerosol inhalation	ChiCTR2000029975 http://www.chictr.org.cn/showproj.aspx?proj=49592	Jilin, China	Single arm study of 10 patients; severity is not defined.	Viral negative-transforming time; 30-day cause-specific mortality	Not yet recruiting; From2020-02-24 To 2020-05-31	Low
Phosphoric chloroquine	ChiCTR2000030031; http://www.chictr.org.cn/showproj.aspx?proj=49806	Guangdong, China	A randomised, double-blind, parallel, controlled trial N=120 patients with mild and moderate covid-19 randomised to phosphoric chloroquine (n=80) or placebo (n=40)	Time of conversion to be negative of novel coronavirus nucleic acid	Recruiting; From2020-02-20 To 2021-03-20	Medium
Hydroxychloroquine sulfate vs chloroquine phosphate	ChiCTR2000030054 http://www.chictr.org.cn/showproj.aspx?proj=49869	Hubei, China	Randomised, Open-label, Parallel, Controlled Trial N=100 with mild or moderate covid-19 randomised to Hydroxychloroquine sulfate (n=40), or phosphate chloroquine (n=40),	Clinical recovery time, time frame 28 days	Not yet recruiting; From2020-02-17 To 2020-05-21	Low

			or routine treatment (n=20)			
Hydroxychloroquine	ChiCTR2000029760 http://www.chictr.org.cn/showproj.aspx?proj=49369	Chongqing	Randomised controlled study N=240 Patients with mild or moderate infectious disease	Time to clinical recovery	Low Cancelled due to lack of patients	Low
Chloroquine	ChiCTR2000029803 http://www.chictr.org.cn/showproj.aspx?proj=49428	Hubei, China	Prevention. Prospective, randomised, open-label, controlled clinical study to evaluate the preventive effect of hydroxychloroquine on close contacts after exposure (COVID-19) 320 patients randomised to hydroxychloroquine small dose, high dose, abidol small dose or abidol high dose	Number of patients who have progressed to suspected or confirmed within 24 days of exposure to new coronavirus	Not yet recruiting; From2020-02-20 To 2021-02-20	Low

Outras abordagens ou estratégias terapêuticas[26]

- Oseltamivir
- Umifenovir (Arbidol)
- Darunavir + Cobicistat
- Azivudine
- Triazavirin
- Fingolimod
- Pirfenidone (Esbriet) (importante)
- Terapia celular com células estaminais, células NK, macrófagos Tipo I
- Fármacos imunomoduladores – glucocorticoides, metilprednisolona, corticosteroides; interferão alfa1beta, interferão, Novaferon
- Imunoglobulinas incluindo plasma inactivado anti-vírus SARS-CoV-2 de convalescentes
- Anticorpos monoclonais – Meplazumab, Bevacizumab, Eculizumab (Soliris), Tocilizumab (importante), vMIP, anticorpo monoclonal anti PD-1
- Polyinosinic:polycytidylic acid
- Thymosin
- Tranilast
- Granulocyte colony-stimulating factor
- Ruxolitinib (Jakavi) + stem cell therapy
- Jakotinib
- ACE-2
- Óxido de azoto
- ECMO
- Perfusão de Vitamina C
- Microbiota
- Probióticos
- Talidomida
- Escinato de sódio
- GD31 (análogo nucleósido)
- Suramina sódica

[26] Danish Medicines Agency - Planned and ongoing clinical studies of drugs for the treatment of COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx

Prevenção de COVID-19

Lista atualizada dos Ensaios Clínicos em curso ou planeados com vacinas para o COVID-19

(fonte: Site da agência Dinamarquesa - Versão 10.03.2020 10:00) [27]

Promotor, vacina	ID estudo	Local estudo	Desenho estudo	Outcome primário	Estado ensaio
Sponsor: National institute of Allergy and Infectious diseases; Moderna Therapeutics;	https://clinicaltrials.gov/ct2/show/NCT04283461 NCT04283461	United States, Washington	Phase 1 open label dose ranging study of the safety and immunogenicity of 2019 nCoV vaccine (mRNA1273) in healthy adults N=45, 3 arm study 25 mcg, 100 mcg, 250 mcg	Relevant safety outcomes; 12 months follow-up	Not yet recruiting Estimated study completion: June 2021
Sponsor: Shenzhen Geno-Immune Medical Institute	https://clinicaltrials.gov/ct2/show/NCT04276896?term=NCT04276896&draw=2&rank=1 NCT04276896	China, Guangdong	Phase 1 and phase 2 Multicenter Trial of Lentiviral Minigene Vaccine (LV-SMENP) of Covid-19 N=100 with confirmed covid-19 infection	Clinical improvement based on the 7-point scale [Time Frame: 28 days after randomization] Lower Murray lung injury score [Time Frame: 7 days after randomization]	Recruiting; Estimated primary completion/estimated primary completion: July 31, 2023/ Dec 31, 2024
Inactivated mycobacterium vaccine Sponsor: Guangxi medical university	ChiCTR2000030016 http://www.chictr.org.cn/showproj.aspx?proj=49799	Guangxi Zhuang, China	N=60 with Covid-19 pneumonia randomized to vaccine or ???	viral negative-transforming time;30-day cause-specific mortality;30-day cause-adverse events;30-day all-cause mortality;co-infections;Time from severe and critical patients to clinical improvement;	Recruiting Dec 12, 2022

[27] Danish Medicines Agency - New coronavirus (COVID-19) - Planned and ongoing clinical studies of vaccines for COVID-19, version 11.03.2020; https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/3A4B7F16D0924DD8BD157BBE17BFED49.ashx

Procedimento por entidades de saúde para casos graves alertando para o acesso muito limitado à data a estas opções terapêuticas.

A utilização de medicamentos em investigação é enquadrável no disposto na alínea a) do n.º 1 do artigo 92.º do Decreto-Lei n.º 176/2006, de 30 de agosto, na sua atual redação, correspondendo a uma Autorização de Utilização Excecional (AUE) individual requerida por uma instituição de saúde. O pedido de utilização de um medicamento ainda não autorizado no Espaço Económico Europeu é submetido por entidade hospitalar que reconhece uma decisão clínica pelo médico assistente que entende não existir alternativa terapêutica ao caso concreto e específico e apresentando ao INFARMED fundamentação clínica que justifique a sua escolha.

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