COVID-19 Clinical Research Coalition

COVID-19 *Clinical Research Coalition*
Tratamentos investigados no combate à COVID-19

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COVID-19 Clinical Research Coalition

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http://boletim.sbq.org.br/noticias/2020/n3479.php

https://www1.folha.uol.com.br/equilibrioesaude/2020/04/cientistas-de-30-paises-incluindo-o-brasil-criam-rede-de-pesquisas-sobre-coronavirus.shtml

Acelerando a pesquisa no COVID-19 em ambientes com recursos limitados

A COVID-19 *Clinical Research Coalition* visa acelerar as necessidades de Pesquisa em COVID-19 nas áreas em que o vírus pode causar estragos em sistemas de saúde já frágeis e causar grande impacto na saúde das populações vulneráveis.

Global coalition to accelerate COVID-19 clinical research in resource-limited settings

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There is no available vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and no drug with proven clinical efficacy, although there are several candidates that might be effective in prevention or treatment. Encouragingly, the response from the research community to the pandemic of coronavirus disease 2019 (COVID-19) has been vigorous. A review of clinical trial registries, as of March 24, 2020, identified 536 relevant registered clinical trials.[1] Of the 332 COVID-19 related clinical trials, 188 are open for recruitment and 146 trials are preparing to recruit.[1,2] The distribution of these clinical trials is centred in the countries most affected by COVID-19 in the past 2 months, particularly China and South Korea, with high-income countries in Europe and North America planning most of the forthcoming trials. Very few trials are planned in Africa, south and southeast Asia, and central and South America.

The number of confirmed COVID-19 cases reported in resource-poor settings is still relatively small,[3] but the availability of testing is also low and numbers of COVID-19 cases are expected to rise substantially in the coming weeks. The capacity of weak health-care systems to manage a surge of severe pneumonia is limited, and the low availability of appropriate personal protective equipment (PPE) for front-line health-care staff means that these key staff are likely to be disproportionately affected by COVID-19. Disruption or complete breakdown of those health-care systems would result in high direct and indirect mortality since care of all illness would be affected.

COVID-19 trials should be adequately powered to generate evidence. They need to be large and well designed. Priority should be given to interventions that reflect the specific needs of countries and are readily implementable. For resource-poor settings, that means interventions need to be affordable and available, and adaptable to the health-care systems and the populations they serve. The adverse impacts of COVID-19 on health and welfare are likely to be considerable in low-income or middle-income countries (LMICs). Clinical trials, and evaluations of affordable and implementable interventions of all types—behavioural, organisational, medical, and supportive—are a priority.[4]

On March 18, 2020, the Director-General of WHO announced the launch of the SOLIDARITY trial, an international study of potential treatments for COVID-19 to be conducted in Asia, South Africa, Europe, and the Americas.[5] WHO has an important convening role in setting COVID-19 research priorities, facilitating trials, and coordinating efforts. The WHO COVID-19 research and development blueprint[6] and the R&D Blueprint Scientific Advisory Group will provide guidance and ensure the necessary coordination and sharing of information. WHO will also have a central role in reviewing the evidence generated by trials and in producing guidelines. Yet despite these international efforts, there remain substantial organisational and bureaucratic obstacles to a rapid research response. Strong political support, effective collaboration, adequate expertise and resources, and informed guidance will be needed to overcome these barriers.

Managing COVID-19 will place considerable pressures on health-care systems. COVID-19 results in severe pneumonia and death in approximately 4–5% of patients admitted to hospital in well supported health-care settings.[3,7] Evidence is needed on pre-exposure prevention, post-exposure prevention, and patient management. Several countries are already recommending chemoprevention or treatments for which there is no convincing evidence of benefit and banning export of these medicines,

Michele Cattani/Getty Images

For the **COVID-19 Therapeutics Accelerator** see https://www.gatesfoundation.org/MediaCenter/Press-Releases/2020/03/COVID-19-Therapeutics-Accelerator

For the **Coalition for Epidemic Preparedness Innovations** see https://cepi.net/covid-19/

For the **SARS-CoV-2 Diagnostic Pipeline** see https://www.finddx.org/covid-19/pipeline/

thereby compromising the trials needed to establish the evidence. It is possible that none of the current therapeutic interventions being trialled or recommended will prove beneficial. Large, well conducted clinical trials are needed urgently to support guidelines on prevention and clinical management. These trials must not detract from already overstretched health services and, with travel bans in many places, they must be designed to accommodate remote initiation and monitoring. There is also much that might be improved in supportive care and organisation in LMIC settings that could reduce direct and indirect COVID-19 morbidity and mortality. Research is needed now to guide the increasingly difficult choices that resource-limited health-care systems will face. Yet additional challenges that relate to ethics review, regulation, manufacturing, clinical trial support and logistics, open science and data sharing, and equitable and affordable access will need to be overcome for these studies to be successful.

The 2013–16 outbreaks of Ebola virus disease in west Africa showed the ethical challenges of doing research in the context of a Public Health Emergency of International Concern. Lessons learned—eg, shortcomings in community engagement, access to basic care, and front-line worker welfare—will need to be applied to the COVID-19 pandemic. Ethics committees and review boards in many countries are unprepared for applications that require rapid review.[8,9]

Regulatory clearance, including importation of products, is required for many drug and vaccine trials and, as for ethical review, this can be very slow. Accelerated clearance pathways for COVID-19 studies such as those recently set up by WHO, the European Medicines Agency, the UK Medicines and Healthcare products Regulatory Agency, and the US Food and Drug Administration are needed in all countries where trials will be held.

In terms of manufacturing, preparation of clinical trial medicines and vaccines might require new doses or formulations and placebos. Many LMIC settings will not have ready access to suitable Good Manufacturing Practice (GMP) manufacturers, and those that do have access may need support in ensuring quality assurance and obtaining regulatory approvals. This also applies to validated diagnostics.

There is tension between the maximum recommended and minimum essential requirements to conduct a good trial. In LMIC settings, the infrastructure required to support clinical trials—eg, preparation of trial products, materials, protocols, case report forms, databases, statistical support, monitoring, and reporting—is seldom readily available. Facilities for laboratory measurement and microbiology identification are often insufficient in these settings[10] and might soon become unavailable because of the COVID-19 pandemic. Essential clinical trial materials are unavailable in many areas, with PPE to protect staff and swabs to obtain nasal and pharyngeal samples for virus identification both in short supply. Some countries forbid export of laboratory samples.

Much of the public and private research is being funded by governments and charities. These funding agreements must mandate open collaboration and data sharing while protecting the rights of participants and patients.[11] Open science and data sharing principles need to be applied at all stages of COVID-19 research to accelerate progress. This includes research undertaken by the private sector. The FAIR guiding principles (Findability, Accessibility, Interoperability, and Reusability) for data should be implemented, and mechanisms put in place to enable equitable use and reuse of data.[12] Evidence will need to be shared with WHO for review and development of policies in line with WHO's normative role.

If interventions are shown to be effective, there should be specific commitments to ensure that they are made available as soon as possible. There should be commitments to, and provisions for, equitable and affordable access.

To address these challenges and accelerate the research needed in resource-limited settings, we propose an international research coalition that brings together existing multinational, multidisciplinary expertise and clinical trial capacity. The coalition will synergise with existing initiatives, such as the COVID-19 Therapeutics Accelerator, the Coalition for Epidemic Preparedness Innovations (CEPI), and the SARS-CoV-2 Diagnostic Pipeline. Our objective is to use our existing research capabilities to support, promote, and accelerate multicentre trials of the safety, efficacy, and effectiveness of interventions against COVID-19 in resource-limited settings. For therapeutics, research in such settings should focus primarily on evaluation of affordable repurposed medicines—ie, those already developed and approved for other indications—and implementable supportive measures. If applicable, testing of new diagnostic tools,

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30798-4/fulltext

A distribuição de ensaios clínicos está centrada nos países mais afetados pela COVID-19, China, Coréia do Sul e países de alta renda na Europa e América do Norte.

Pouquíssimos ensaios estão planejados na África, sul e sudeste da Ásia, e América Central e do Sul.

A capacidade de sistemas de saúde fracos para gerenciar uma onda de pneumonia grave é limitada, com baixa disponibilidade de pessoal treinado e de equipamentos de proteção Individual (EPI) para os profissionais de saúde na linha de frente, muito afetados pela COVID-19.

Sudão do Sul: população de 12 milhões, tem 4 respiradores e 24 leitos de UTI
Burkina Faso: tem 11 respiradores, população de 19,7 milhões.
Serra Leoa: Com 7,6 milhões de habitantes, tem 13 respiradores.
República Centro-Africana: com 4,6 milhões de habitantes, possui 3 respiradores.
Venezuela: possui 84 leitos de UTI para 32 milhões de habitantes.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30798-4/fulltext

Os ensaios com COVID-19 em ambientes com poucos recursos precisam ser acessíveis, disponíveis e adaptáveis aos sistemas de saúde e às populações a que servem.

Em 18 de março de 2020, o Diretor-Geral da OMS anunciou o lançamento do estudo SOLIDARITY, um estudo internacional de possíveis tratamentos para a COVID-19 a ser realizado na Ásia, África do Sul, Europa e Américas.

Identificar e recomendar opções que garantam o acesso justo, transparente e eficiente a medicamentos, equipamentos e futuras vacinas, em especial em países em desenvolvimento.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30798-4/fulltext

Os princípios da ciência aberta e do compartilhamento de dados precisam ser aplicados em todas as etapas da pesquisa da COVID-19 para acelerar o progresso, protegendo os direitos dos participantes e pacientes.

O documento também pede para que as nações e outros grupos interessados tomem ações legais para impedir o acúmulo e especulações que podem limitar o acesso de outros aos medicamentos e equipamentos, uma coordenação mais eficiente com o setor privado, para a produção de medicamentos antivirais, equipamentos de produção e testes diagnósticos.

COVID-19 Clinical Research Coalition

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I pledge my support

#covid19crc

All interventions that prove to be effective for COVID-19 must be affordable and available in low-resource settings

www.covid19crc.org

COVID-19 Clinical Research Coalition

Os países do G-20 tem o dever moral de serem solidários com países Africanos e todos os países com populações vulneráveis

Members

Members of the COVID-19 Clinical Research Coalition include:

- Addis Ababa University, Ethiopia – Tassew Woldehanna
- ALIMA, France – Augustin Augier
- American Society of Tropical Medicine and Hygiene (ASTMH), USA – Joel G Breman
- Aurum Institute, South Africa – Gavin Churchyard
- Baylor College of Medicine, USA – Maria Elena Botazzi, Peter Hotez
- Bill & Melinda Gates Foundation, USA – Trevor Mundel
- Botnar Foundation, Tanzania – Hassan Mshinda
- CDT-Africa, Addis Ababa University, Ethiopia – Abebaw Fekadu
- CEADES Foundation, Bolivia – Faustino Torrico
- Center for Disease Dynamics, Economics & Policy, USA – Ramanan Laxminarayan
- Christian Medical College, Vellore, India – George M Varghese

- Clinical Research Malaysia, Malaysia – Yussof Ahkmal
- Critical Care Asia Network, Mahidol Oxford Tropical Medicine Research Unit, Thailand – Arjen Dondorp
- Drugs for Neglected Diseases initiative, Switzerland – Marie-Paule Kieny, Bernard Pécoul, Nathalie Strub-Wourgaft
- DZIF German Center for Infection Research, Germany – Maura Dandri, Dirk Heinz, Timo Jaeger, Hans-Georg Kraeusslich
- Epicentre, France – Emmanuel Baron
- ETHOX Centre, University of Oxford, UK – Michael Parker
- FIND, Switzerland – Catharina Boehme
- Fundação Oswaldo Cruz (Fiocruz), Brazil – Nísia Trinidade Lima
- GARDP, Switzerland – Manica Balasegaram
- Ghana Health Service, Ghana – Abraham Hodgson
- Harvard Medical School, USA – Paul Farmer
- Huesped Foundation, Argentina – Pedro Cahn, Omar Sued
- icddr, b, Bangladesh – John Clemens
- Ifakara Health Institute, Tanzania – Honorati Masanja
- Infectious Diseases Data Observatory (IDDO), University of Oxford, UK – Philippe J Guerin
- Institut National pour la Recherche Biomédicale, Democratic Republic of Congo – Jean-Jacques Muyembe
- Institute of Endemic Diseases, University of Khartoum, Sudan – Muntaser Ibrahim
- Institute of Global Health, University of Geneva, Switzerland – Antoine Flahault
- Institute of Tropical Medicine, Belgium – Marc-Alain Widdowson
- Instituto Nacional de Salud de Colombia, Colombia – Marcela Mercado, Marta Ospina
- International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), UK – Gail Carson
- ISARIC & the African Coalition for Epidemic Research, Response and Training (ALERRT), UK – Peter Horby

- ISGlobal, Spain – Denise Naniche, Antonio Plasència Taradach
- Karolinska Institutet, Sweden – Anders Björkman
- KEMRI-Wellcome Trust Research Programme, Kenya – Philip Bejon, Yeri Kombe
- Kenya Pharmacy & Poisons Board, Kenya – Fred Siyoi
- Liverpool School of Tropical Medicine, UK – David Lalloo
- Mahidol Oxford Tropical Medicine Research Unit, Thailand – Nick Day, Nicholas J. White
- Mahidol University, Thailand – Prasert Auewarakul
- Makerere University, Uganda – Barnabas Nawangwe
- Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi – Steven Gordon
- Medicines for Malaria Venture, Switzerland – David Reddy
- Menzies School of Health Research, Australia – Richard Price
- Ministry of Health, Malaysia – Noor Hisham Abdullah
- Mundo Sano Foundation, Argentina – Marcelo Claudio Abril
- National Academy of Medicine of Buenos Aires, Argentina – Roberto Chuit
- National Administration of Laboratories and Health Institutes of Argentina (ANLIS), Argentina – Martin Avaro, Elsa Baumeister, Estafanio Benedetti, Andrea Pontoriero, Maro Russo
- Nigeria Centre for Disease Control, Nigeria – Chikwe Ihekweazu
- Norwegian Research Council, Norway – John Arne Røttingen
- Nuffield Council of Bioethics, UK – Katharine Wright
- Oxford University Clinical Research Unit, Vietnam – Guy Thwaites
- Pan-African Network for Rapid Research Response Relief and Preparedness for Infectious Disease Epidemics (PANDORA-ID-NET), Fondation Congolaise pour la Recherche Médicale, Brazzaville, Republic of Congo – Francine Ntoumi
- Partners in Health, USA – Joia Mukherjee

- Pasteur Institute, France – Stewart Cole
- REACTing & INSERM, France – Yazdan Yazdanpanah
- Société Francophone de Médecine Tropicale et Santé Internationale, France – Jean Jannin
- South African Medical Research Council, South Africa – Charles S Wiysonge
- Swiss Academy of Arts and Sciences, Switzerland – Marcel Tanner
- Swiss Tropical and Public Health Institute, Switzerland – Jürg Utzinger
- The African coalition for Epidemic Research Response and Training (ALERRT), Kwame Nkrumah University of Science and Technology, Ghana – John H Amuasi
- The Global Health Network, UK – Trudie Lang
- Translational Health Science and Technology Institute of India, India – Gagandeep Kang
- UCSF, USA – Philip J Rosenthal
- UK Public Health Rapid Support Team & London School of Hygiene & Tropical Medicine, UK – Daniel G. Bausch
- UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Switzerland – John Reeder
- Universidad Peruana Cayetano Heredia, Peru – Patricia Garcia
- University of Campinas, Brazil – Munir S. Skaf
- University of Gondar, Ethiopia – Ashenafi Tazebew Amare
- University of Nairobi, Kenya – Anastasia Guantai
- Wellcome, UK – Jeremy Farrar

E O BRASIL...???

Com o apoio de 179 países, a Assembleia Geral da ONU adotou uma resolução demandando uma ação global para acelerar rapidamente o desenvolvimento, a produção e o acesso à medicamentos, vacinas e equipamentos médicos frente ao novo coronavírus.

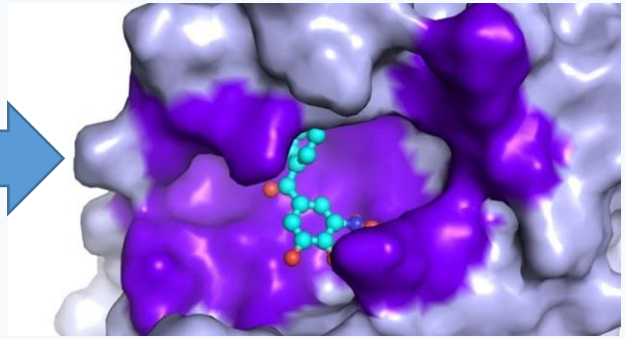
O Brasil, ao lado dos Estados Unidos, da Hungria, do Irã e da Rússia, está entre os 14 Estados-membros que não patrocinaram a medida.

Tratamentos investigados no combate à COVID-19

Para os cientistas, é fundamental saber se estes medicamentos funcionam para a COVID-19, se são seguros, qual a dose segura, quais pacientes podem ser tratados, em qual fase da doença podem ser aplicados, se podemos produzir no Brasil para conter este surto, sempre lembrando que é fundamental manter o foco nos tratamentos de suporte, no isolamento social, em testes de diagnóstico, leitos de UTI e respiradores para desafogar o sistema de saúde.

Fluxograma simplificado das etapas da estratégia de reposicionamento de fármacos

Fármacos disponíveis,
já aprovados para diferentes
aplicações terapêuticas

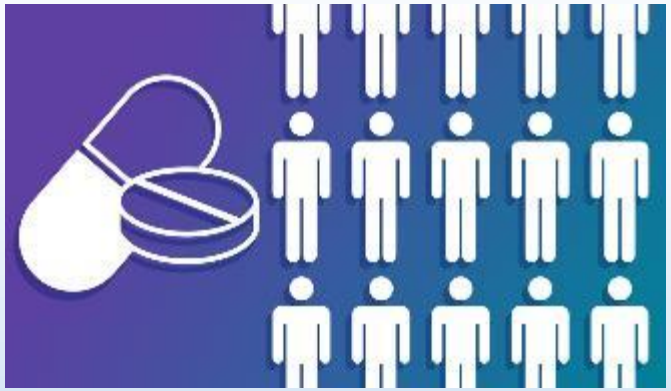


Estudos computacionais
(em proteínas específicas)

Testes *in vitro*
(em cultura de células)

**Faltam investimentos em
testes em animais para COVID-19**

Ensaios *in vivo*, em modelo animal.
(Nem sempre disponíveis)



Triagens clínicas (fases I, II, III e IV).
Na fase IV o medicamento já foi lançado,
É também chamada fase de farmacovigilância

Marco Edilson Freire de Lima
Professor Titular
Universidade Federal Rural do Rio Janeiro (***UFRRJ***)

TAMIFLU (OSELTAMIVIR)

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Em quatro meses de epidemia, entre os fármacos já deixados para trás, está o Tamiflu (oseltamivir), desenhado especificamente para combater influenza (H1N1).

O uso de corticoides para tentar evitar os processos inflamatórios mais nocivos da Covid-19 também falharam.

ROCHE

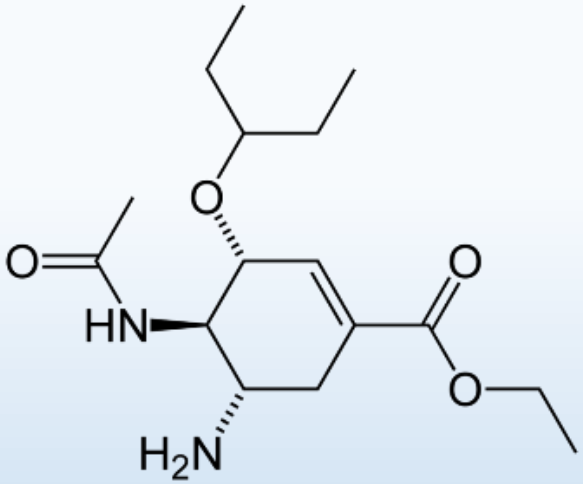
Tamiflu and Use in Coronavirus (COVID-19)

This response corresponds to your request for information on the use of Tamiflu® (oseltamivir phosphate) for the treatment of novel human coronavirus (COVID-19).

This response was developed according to principles of evidence-based medicine and includes information from case series and reports with 5 or more patients.

In Brief

- There are currently no medicines approved to specifically treat human coronaviruses. Tamiflu is designed to be highly specific to the influenza virus. Due to this high specificity, it is extremely unlikely that Tamiflu would be effective at treating the coronavirus.
- Independent laboratory testing conducted by Hong Kong University, School of Public Health demonstrates that Tamiflu does not have any antiviral effect on the novel coronavirus.
- Two case series describe the use of oseltamivir in patients hospitalized for COVID-19 in Wuhan, China.



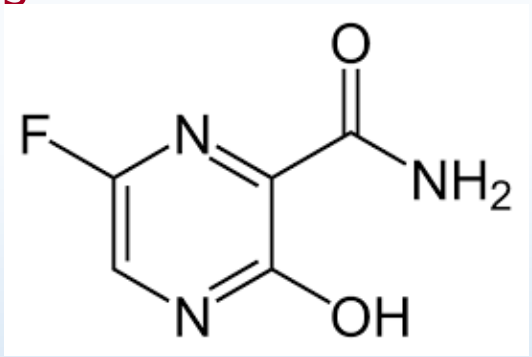
FAVIPIRAVIR

Medicamento antiviral usado para tratar a gripe na China, aprovado em **15 de fevereiro de 2020**.

A Toyama Chemical anunciou o início dos testes clínicos do medicamento Avigan (favipiravir) para avaliar a eficácia contra o novo coronavírus SARS-CoV-2, após resultados interessantes *in vitro*.

O estudo na fase 3 vai ser avaliado em 100 pacientes contaminados pela COVID-19 até o final de junho.

O fármaco está sendo administrado durante 14 dias para pacientes entre 20 e 74 anos, que apresentam quadro de pneumonia viral, uma complicação típica da infecção por Covid-19.



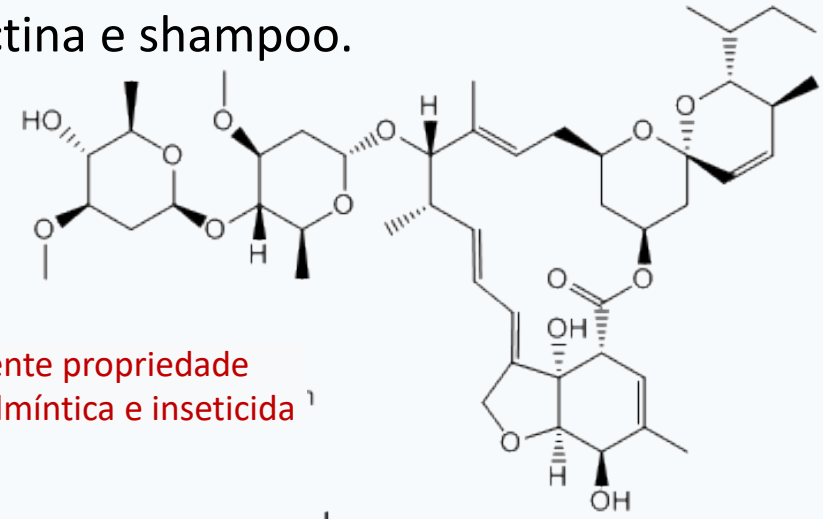
O medicamento apresenta efeitos colaterais importantes como abortos e má-formação fetal e, por isso, não é utilizado em gestantes.

IVERMECTINA

Universidade de Monash, Austrália, antiparasitário foi capaz de inibir SARS-COV-2 em culturas de células infectadas em laboratório (testes *in vitro*)!
Pessoas infestadas de piolhos, tratamento é com ivermectina e shampoo.

Se mostrou eficaz em testes *in vitro* contra uma ampla gama de vírus, como os que causam o HIV, a dengue, a gripe e o Zika.

Causa diarréia e náusea, dor abdominal, anorexia, vômitos, tontura, sonolência, vertigem e tremor.

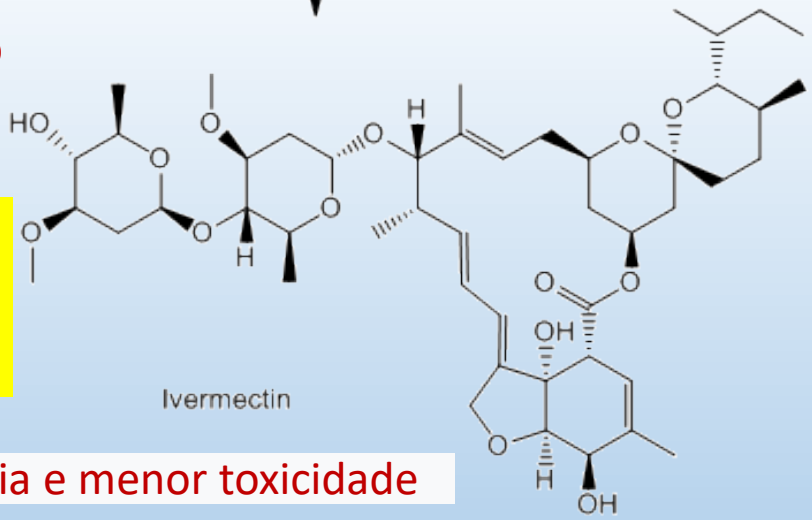


potente propriedade anti-helmíntica e inseticida

Avermectina é produto de fermentação por *Streptomyces avermitilis*, um actinomiceto do solo

O **Prêmio Nobel de Fisiologia ou Medicina** 2015 foi concedido juntamente para Campbell e Ōmura pela descoberta da Avermectina e a Youyou Tu por suas descobertas na terapia contra a malária (Artemisin).

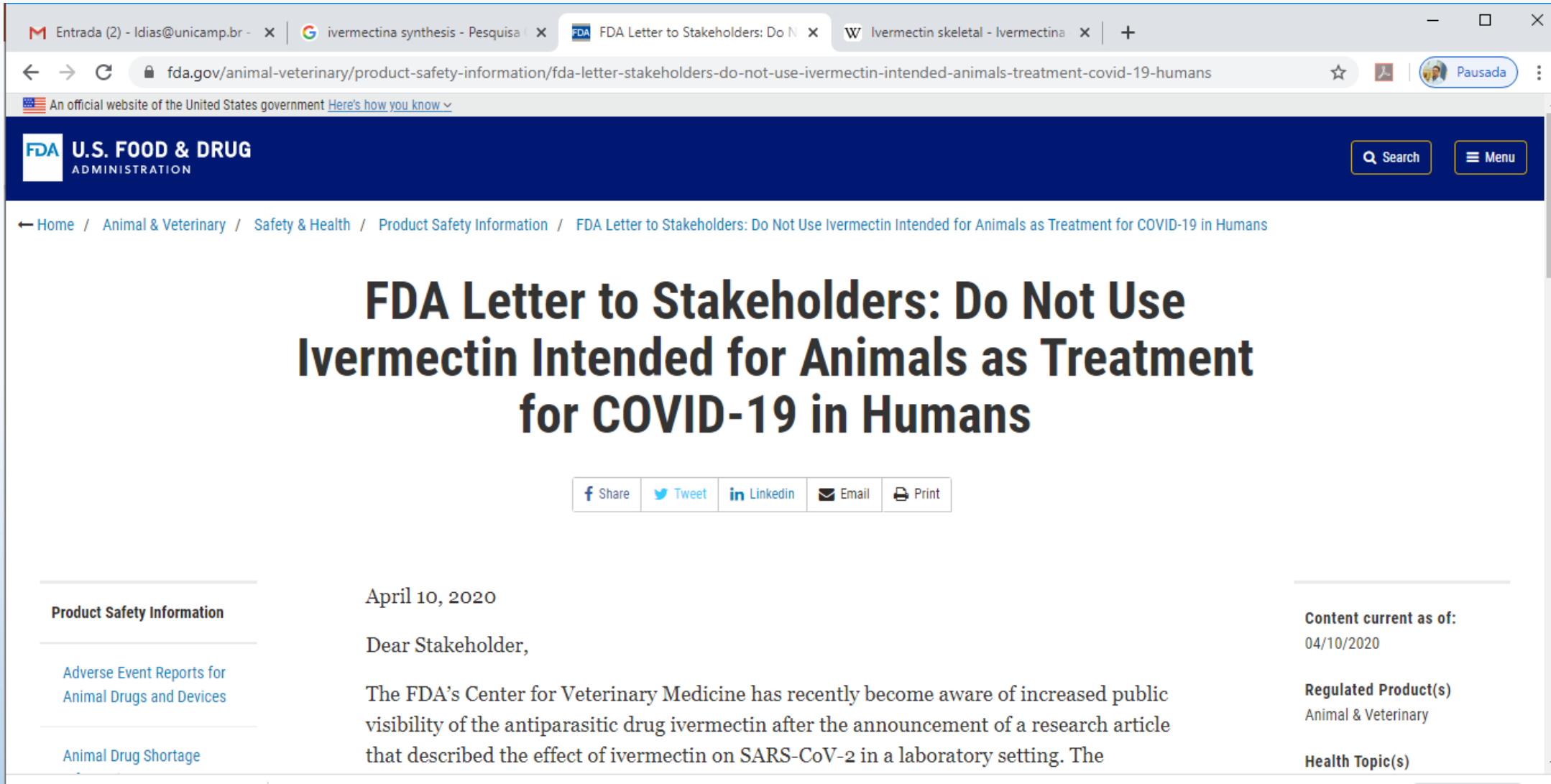
$H_2/RhCl(PPh_3)_3$



Derivado sintetizado em 1975, maior potência e menor toxicidade

A **IVERMECTINA inibe** a replicação de SARS-CoV-2 *in vitro* (em cultura de células de rim de macaco) com um IC_{50} de 2,5 µM. Observe que as doses utilizadas na cultura de células exigiriam doses 10^3 a 10^4 maiores em humanos, o que não parece promissor como tratamento eficaz para o Covid19. Além disso, experimentos em cultura de células também mostraram promessas para o tratamento da infecção pelo vírus Dengue, mas posteriormente falharam em modelos animais.

Em 10/04/2020, o FDA orientou para não usar ivermectina destinada a animais como tratamento para COVID-19 em humanos.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

ABSTRACT

BACKGROUND

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.

RESULTS

A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were assigned to the lopinavir–ritonavir group, and 100 to the standard-care group. Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, –5.8 percentage points; 95% CI, –17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

CONCLUSIONS

In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit. (Funded by Major Projects of National Science and Technology on New Drug Creation and Development and others; Chinese Clinical Trial Register number, ChiCTR2000029308.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cao at caobin_ben@163.com, to Dr. C. Wang at cyh-birm@263.net, or to Dr. D. Zhang at 1813886398@qq.com.

Drs. Cao, Y. Wang, Wen, W. Liu, Jingli Wang, Fan, L. Ruan, Song, Cai, and M. Wei and Drs. D. Zhang and C. Wang contributed equally to this article.

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LOPINAVIR/RITONAVIR

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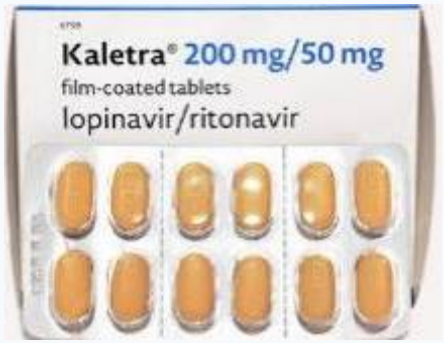
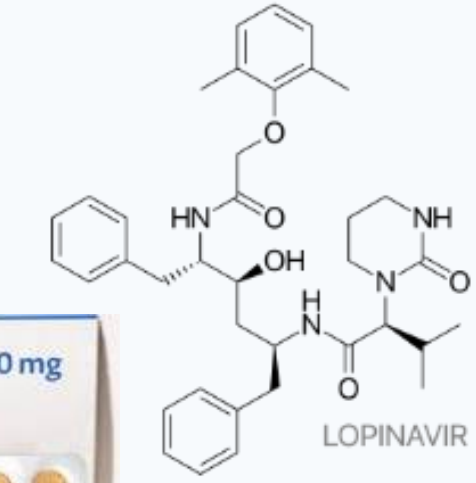
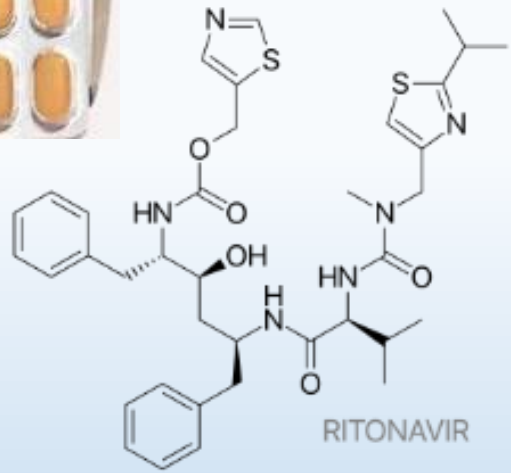
Resultados *in vitro* interessantes







O Lopinavir sofre extenso metabolismo pela CYP3A.
É co-formulado com o inibidor de CYP3A, Ritonavir,
que atua atrasando o metabolismo
do Lopinavir, mantendo alta concentração
plasmática deste.

LOPINAVIR/RITONAVIR

New England Journal of Medicine (NEJM) um ensaio clínico com lopinavir-ritonavir, cujo nome comercial mais conhecido é Kaletra®, 99 adultos com Covid-19 e sinais radiológicos de pneumonia viral.

Ensaio com grupo controle (100 pacientes).

Melhora clínica com 14 dias: 45% com medicação vs 30% sem medicação.

Tempo até melhora: 15 dias com medicação vs 16 dias no controle.

Mortalidade: 19,2% com medicação vs 25% no controle (não significativo, p>0,05).

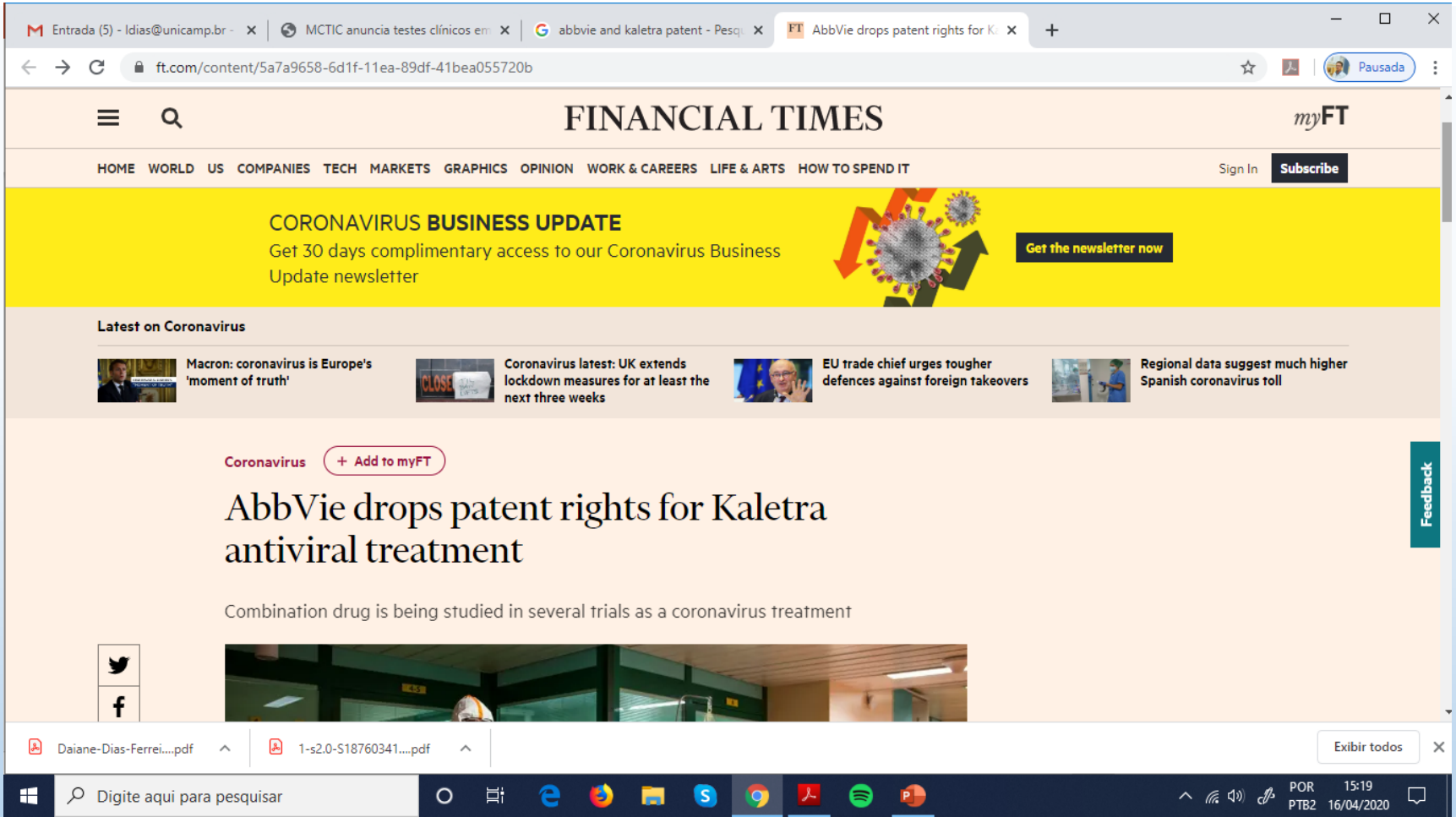
13 pacientes interromperam tratamento antes por efeitos colaterais adversos, como gastrointestinais.

No editorial, os autores são céticos, pois apesar de alguns sinais de melhora clínica, não houve redução da viremia, o que na opinião deles poderia indicar algum viés.

LOPINAVIR/RITONAVIR

CONCLUSIONS

In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit. (Funded by Major Projects of National Science and Technology on New Drug Creation and Development and others; Chinese Clinical Trial Register number, ChiCTR2000029308.)



HIDROXICLOROQUINA/AZITROMICINA

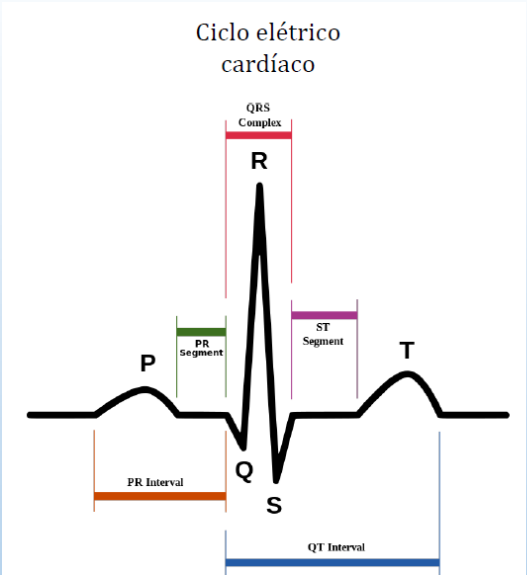
UNICAMP

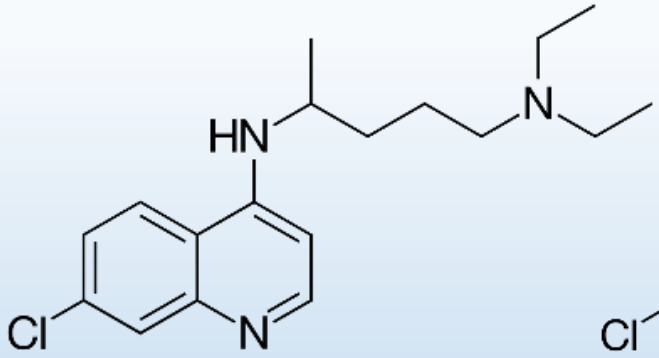
Estudos clínicos multicêntricos, tem bastante tempo de farmacovigilância. Diante da demanda da população, alguns países se apressam em apresentar alternativas terapêuticas, sem que haja comprovação científica, como o caso da cloroquina combinada com azitromicina.

Há inúmeros riscos nessa estratégia. As tomadas de decisão devem ser baseadas em resultados sólidos, conduzidos respeitando o rigor da ciência.

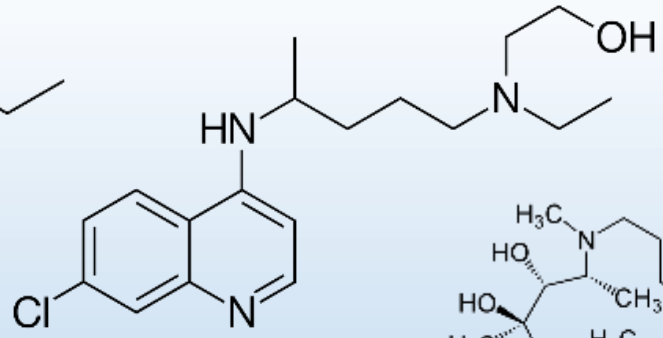
A cloroquina é utilizada no Brasil para tratamento de malária causada *pelo Plasmodium vivax* e a hidroxicloroquina é um medicamento utilizado para tratamento de artrites e lúpus.

Ninguém deve usar estes medicamentos esperando um efeito de proteção, profilático, pois não são vacinas. Estes medicamentos podem ser altamente tóxicos em dose alta, pois eles interferem no intervalo QT, causando problemas cardíacos, cegueira e morte.



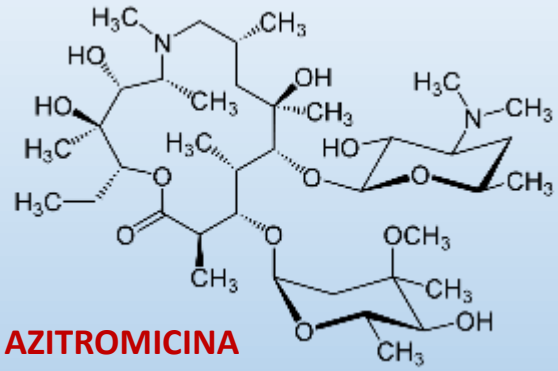


CLOROQUINA
(Síntese em 1934)



HIDROXICLOROQUINA
(Síntese em 1946)

hERG – alta basicidade



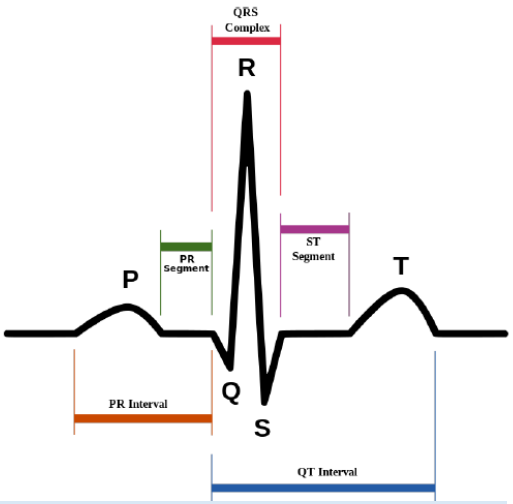
AZITROMICINA

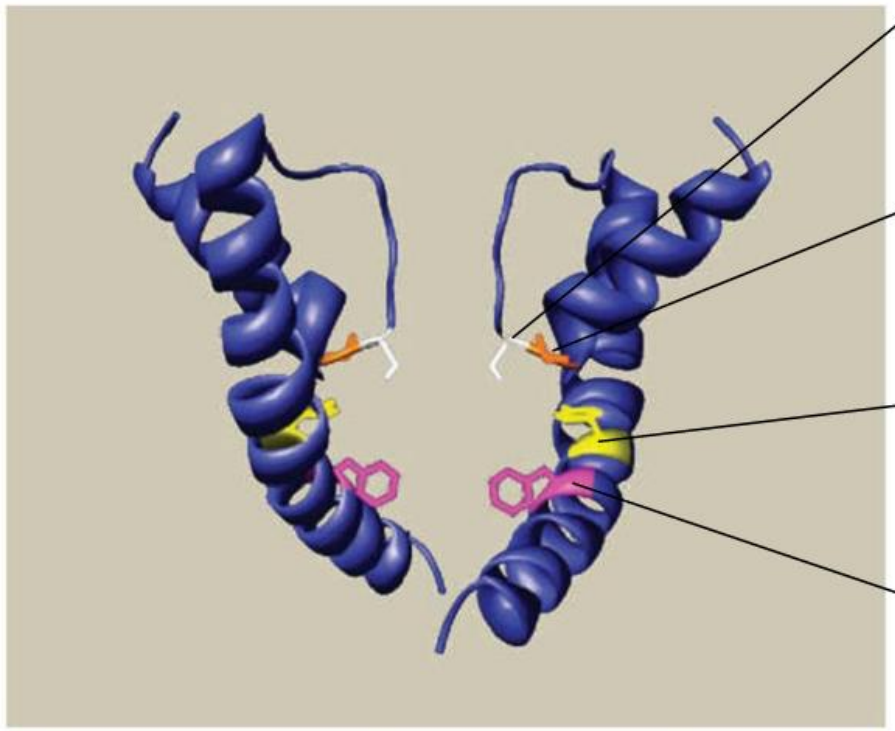
Canal hERG

Principais resíduos de interação

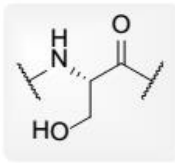
UNICAMP

Ciclo elétrico cardíaco

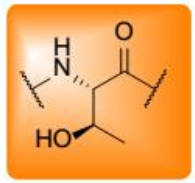




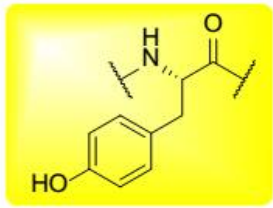
Ser624



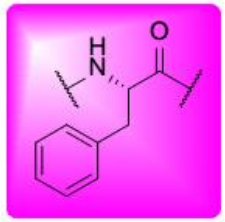
Thr623



Tyr652



Phe656



Sanguinetti & Tristani-Firouzi, *Nature* 440, 463, **2006**

(210) Disney on Broadway 25th | Entrada (5) - ldias@unicamp.br | Cientistas interrompem estudo

noticias.r7.com/saude/cientistas-interrompem-estudo-com-cloroquina-apos-morte-de-pacientes-14042020

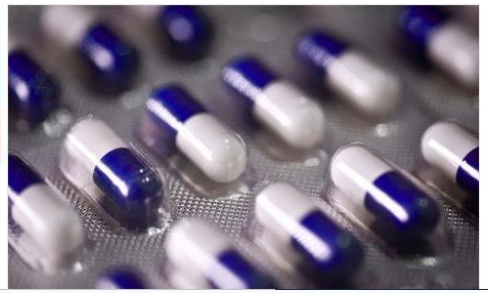
R7 SAÚDE | Cientistas interrompem estudo com cloroquina após morte de pacientes

Cientistas interrompem estudo com cloroquina após morte de pacientes

Em Manaus, 11 pacientes diagnosticados com a covid-19 morreram após receberem alta dosagem do medicamento

SAÚDE
Do R7
14/04/2020 - 15h43 (Atualizado em 14/04/2020 - 16h21)

A- A+



Um grupo de cientistas brasileiros decidiu interromper os testes realizados com cloroquina para tratamento de pacientes com a covid-19. O cancelamento

O estudo envolveu 81 pacientes na cidade de Manaus.

O cancelamento ocorre após 11 pessoas morreram depois de receberem doses elevadas do medicamento, em torno de 600mg BID.

E não houve benefícios para o grupo que recebeu dosagem de 450 mg BID.

A cloroquina poderia ser usada para diminuir a carga viral nas secreções respiratórias, permitindo menor transmissão hospitalar. No entanto, os resultados não forneceram evidências desse efeito.

A Secretaria de Segurança-Pública do Amazonas (SSP-AM) e a Polícia Civil informaram que investigam ameaças de morte feitas ao médico da Fundação de Medicina Tropical e pesquisador da Fiocruz-AM, Marcus Lacerda.

(210) Disney on Broadway 25th | Entrada (5) - ldias@unicamp.br | Pesquisadores de estudo suspen

saude.estadao.com.br/noticias/geral,pesquisadores-de-estudo-suspenso-sobre-cloroquina-viram-alvo-nas-redes-sociais,70003273899

ESTADÃO Saúde

Pesquisadores de estudo suspenso sobre cloroquina viram alvo nas redes sociais

Redes bolsonaristas classificaram os cientistas como irresponsáveis. Líder de estudo explica que procedimer comitês de ética e recebe apoio do Conselho da Fiocruz

Giovana Girardi, O Estado de S.Paulo
16 de abril de 2020 | 21h01
Atualizado 17 de abril de 2020 | 12h17

ESPECIAL CORONAVÍRUS SAIBA MAIS

Um dos estudos que vinha sendo conduzido com a **cloroquina** em **Manaus** – que foi modificado após observação de aumento de risco de complicações cardíacas – virou alvo em redes bolsonaristas, com os cientistas sendo chamados de irresponsáveis e acusados de usarem "cobaias humanas".

COMO NÃO SE FAZER UM ESTUDO CLÍNICO

UNICAMP

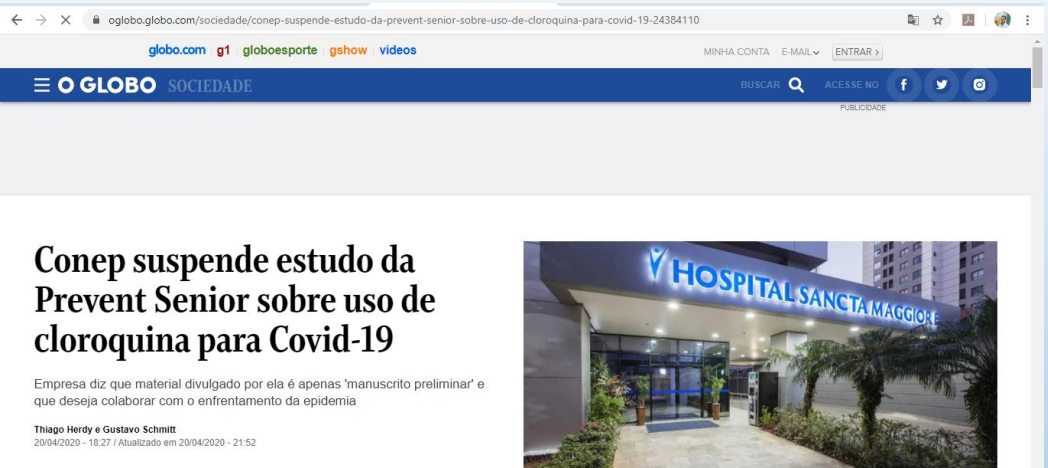
Estudo terrivelmente mal feito e tendencioso

O Prevent Senior estudou um grupo de 721 pacientes, recrutados por telemedicina, com "suspeita" de COVID-19, mas sem qualquer resultado de exame que confirmasse a presença do vírus.

Dos 721 pacientes listados, 85 não foram acompanhados. Sobraram 636.
Desses, 224 se recusaram a receber o tratamento e viraram o grupo de controle.

O grupo analisado que tomou hidroxicloroquina e azitromicina (em doses não conhecidas) teve 412 pessoas.

Estudo: https://static.poder360.com.br/2020/04/2020.04.15-journal-manuscript-final.pdf


oglobo.globo.com/sociedade/conep-suspende-estudo-da-prevent-senior-sobre-uso-de-cloroquina-para-covid-19-24384110

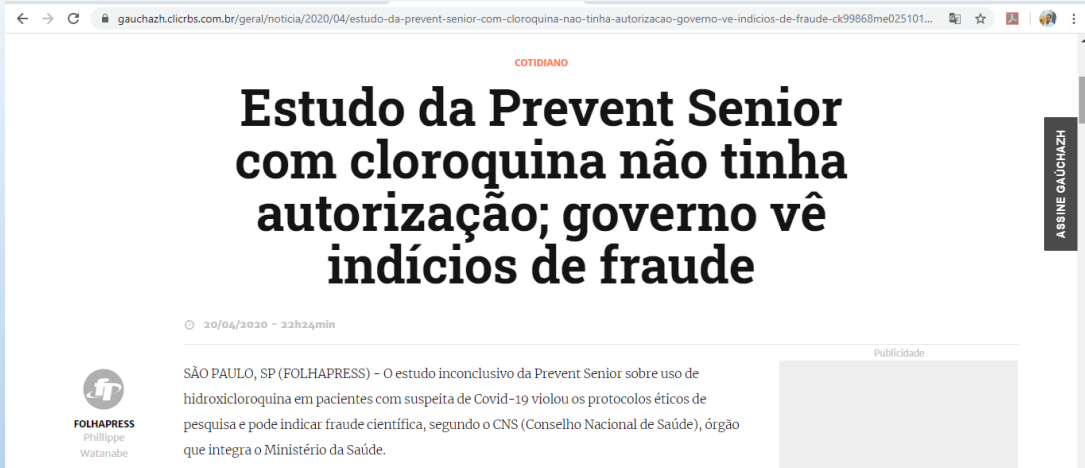
globo.com g1 globoesporte gshow videos

O GLOBO SOCIEDADE

Conep suspende estudo da Prevent Senior sobre uso de cloroquina para Covid-19

Empresa diz que material divulgado por ela é apenas 'manuscrito preliminar' e que deseja colaborar com o enfrentamento da epidemia

Thiago Herdy e Gustavo Schmitt
20/04/2020 - 18:27 / Atualizado em 20/04/2020 - 21:52


gauchazh.clicrbs.com.br/geral/noticia/2020/04/estudo-da-prevent-senior-com-cloroquina-nao-tinha-autorizacao-governo-ve-indicios-de-fraude-ck99868me025101...

COTIDIANO

Estudo da Prevent Senior com cloroquina não tinha autorização; governo vê indícios de fraude

20/04/2020 - 22h24min

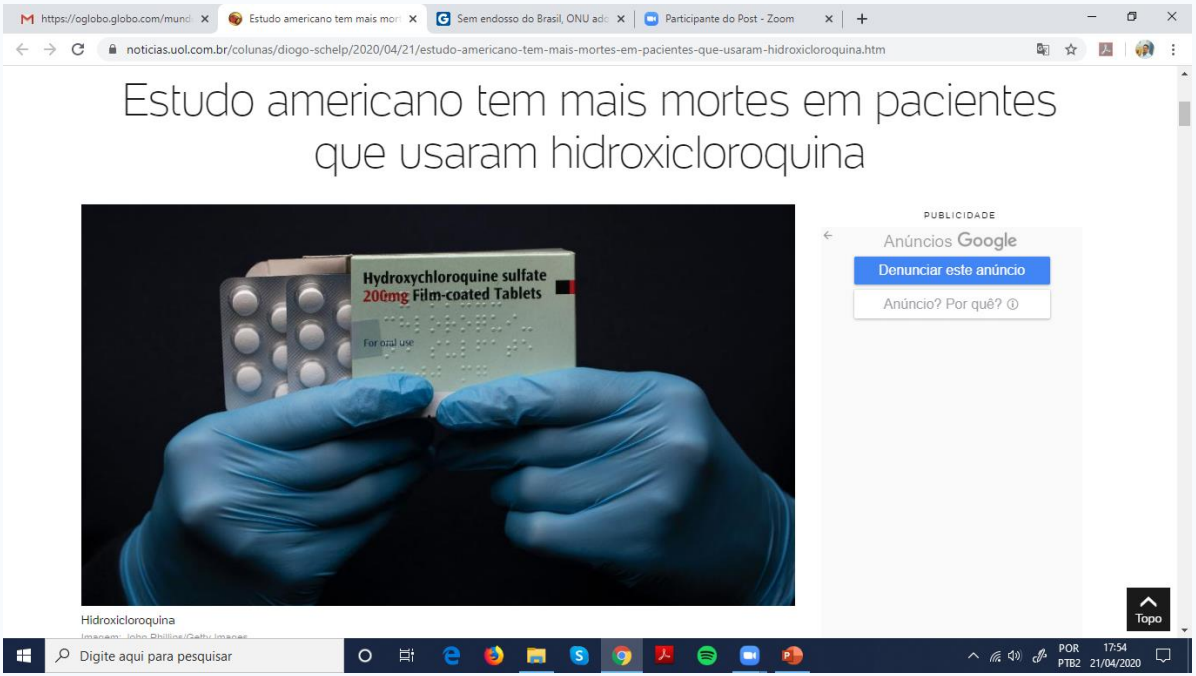
FOLHAPRESS
Phillippe Watanabe

SÃO PAULO, SP (FOLHAPRESS) - O estudo inconclusivo da Prevent Senior sobre uso de hidroxicloroquina em pacientes com suspeita de Covid-19 violou os protocolos éticos de pesquisa e pode indicar fraude científica, segundo o CNS (Conselho Nacional de Saúde), órgão que integra o Ministério da Saúde.

Publicidade

ASSINE GAÚCHAZH

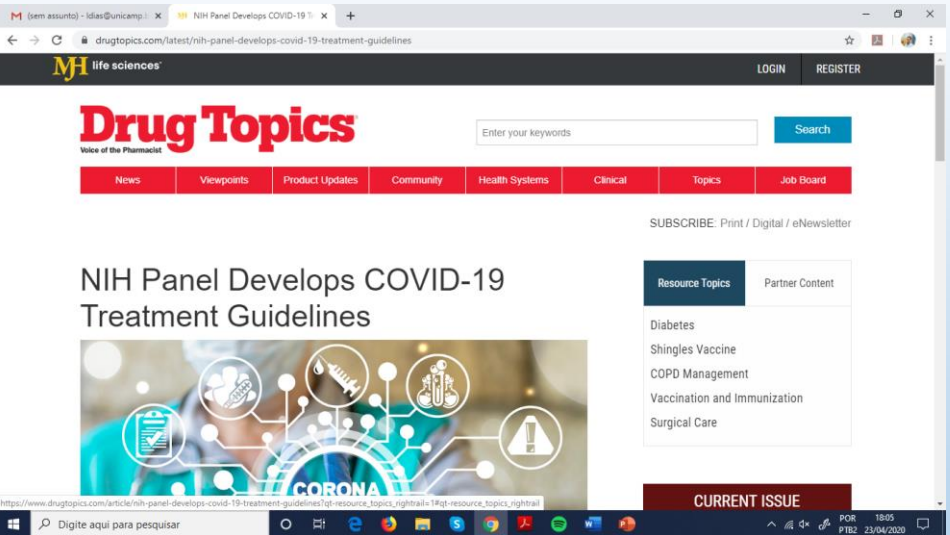
HIDROXICLOROQUINA/AZITROMICINA



Universidade de Virgínia: 368 pacientes infectados com o novo coronavírus.

Não encontraram evidências de que o uso de hidroxicloroquina, com ou sem azitromicina, reduziu o risco de ventilação mecânica em pacientes internados com COVID-19. Uma associação de aumento de mortalidade geral foi identificada em pacientes tratados apenas com hidroxicloroquina.

Com hidroxicloroquina: 27,8% morreram.
Com hidroxicloroquina + azitromicina: 22,1% morreram.
Sem tratamento: 11,4% morreram.



As diretrizes não recomendaram a favor ou contra o uso de cloroquina ou hidroxicloroquina no tratamento de COVID-19. No entanto, eles recomendaram contra o uso de hidroxicloroquina em combinação com azitromicina, devido ao potencial de toxicidade.

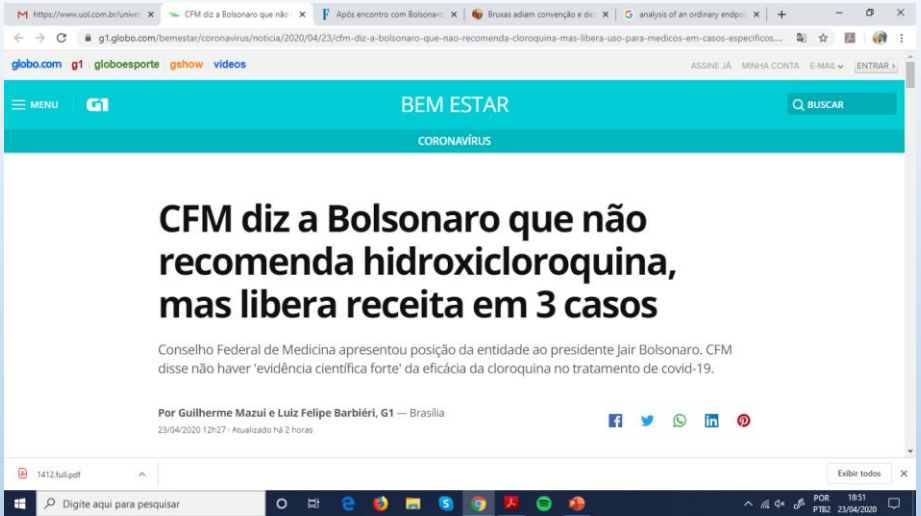
AUTORIZA, MAS NÃO RECOMENDA???

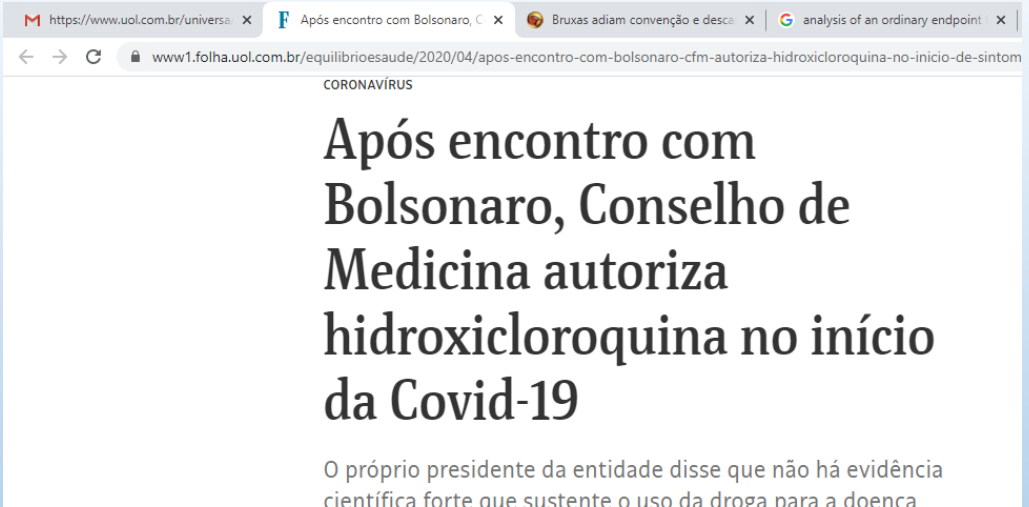
UNICAMP

O Conselho Federal de Medicina (CFM) teve uma reunião com o presidente Jair Bolsonaro e disse que não recomenda o uso da **hidroxicloroquina** para pacientes em tratamento de **COVID-19**.

O órgão decidiu liberar os médicos a receitarem o medicamento em três casos específicos:
1.Quando o paciente está em estado crítico, internado em UTI, com lesão pulmonar. A hidroxicloroquina pode ser usada pelos médicos "por compaixão", quando o paciente já está fora de possibilidade terapêutica e o médico, com autorização da família, utiliza a substância;
2.Quando o paciente, com sintomas da COVID-19, chega ao hospital. Existe um momento de replicação viral em que o medicamento pode ser usado pelo médico com autorização do paciente e familiares;
3.Quando o paciente tem sintomas leves, parecidos com o da gripe comum, o médico pode usar a hidroxicloroquina, descartando a possibilidade de que o paciente tenha: influenza A ou B, dengue, ou H1N1. Também nesse caso, a decisão deve ser compartilhada com o paciente.

"O Conselho Federal de Medicina não recomenda o uso da hidroxicloroquina. O que estamos fazendo é dando ao médico brasileiro o direito de, em decisão compartilhada com seu paciente, utilizar esse medicamento. **Uma autorização, não é recomendação", disse o presidente do CFM, Mauro Luiz de Britto Ribeiro.**





ARBIDOL (Umifenovir)

ARTICLE IN PRESS
JID: YJINF [m5G;April 14, 2020;21:52]
Journal of Infection xxx (xxxx) xxx
Contents lists available at ScienceDirect
Journal of Infection
journal homepage: www.elsevier.com/locate/jinf

Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

Zhen Zhu[a,b,1], Zhaohui Lu[c,1], Tianmin Xu[d], Cong Chen[e], Gang Yang[c], Tao Zha[f], Jianchun Lu[a,g], Yuan Xue[a,g,*]

50 pacientes com COVID-19 confirmados foram divididos em dois grupos: Grupo lopinavir/ritonavir (34 casos) e o Grupo arbidol (16 casos). O grupo lopinavir/ritonavir recebeu 400 mg/100 mg de Lopinavir/ritonavir, duas vezes por dia durante uma semana, enquanto o grupo arbidol recebeu 0,2 g de arbidol, três vezes ao dia.

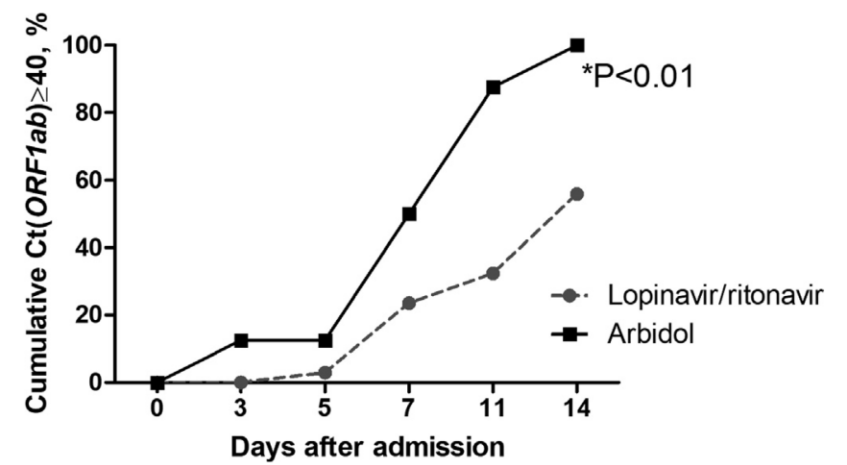
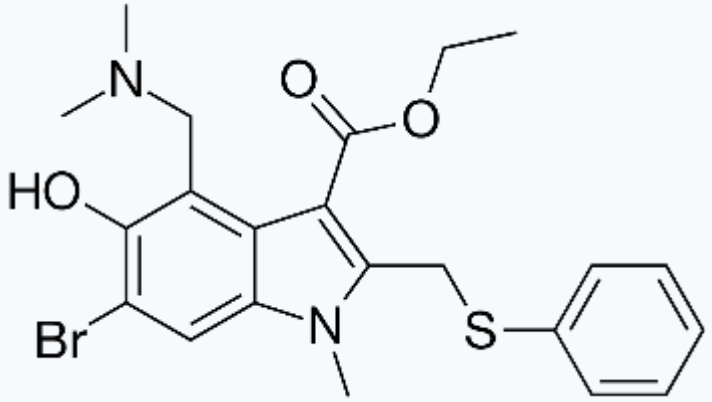


Fig. 1. Dynamic changes of cycle threshold (Ct) values during treatment with lopinavir/ritonavir and arbidol. Ct, cycle threshold.



O umifenovir é um tratamento antiviral para infecção por influenza usado na Rússia e na China.

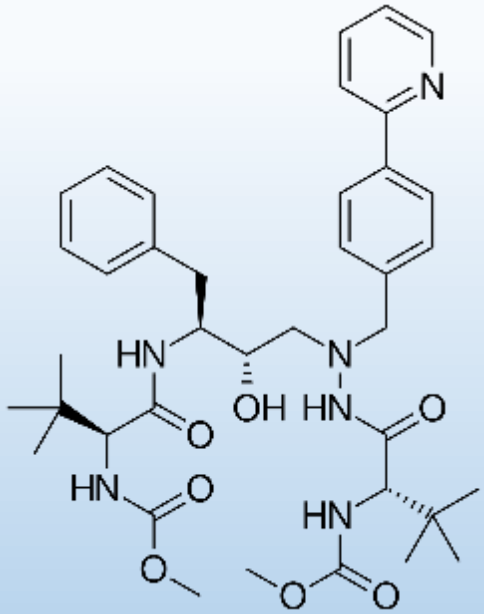
REYATAZ (ATAZANAVIR)

Pesquisadores da **Fiocruz** testaram o Atazanavir contra o coronavírus, que mostrou ser capaz de reduzir em até 100 vezes a velocidade de replicação do vírus Sars-CoV-2.

O experimento foi feito em cultura de células, está sendo testado em humanos. Devido ao histórico com a Aids, esse medicamento é potencialmente menos tóxico do que a cloroquina.

A descoberta não significa que o **Atazanavir** poderá ser empregado imediatamente no tratamento de vítimas da COVID-19,mas tem resultados bons o suficiente para ser testado em estudos maiores. Em tese, ele também pode reduzir a inflamação generalizada associada aos casos mais graves da doença.

Medicamento antiretroviral usado para tratar e prevenir HIV/AIDS

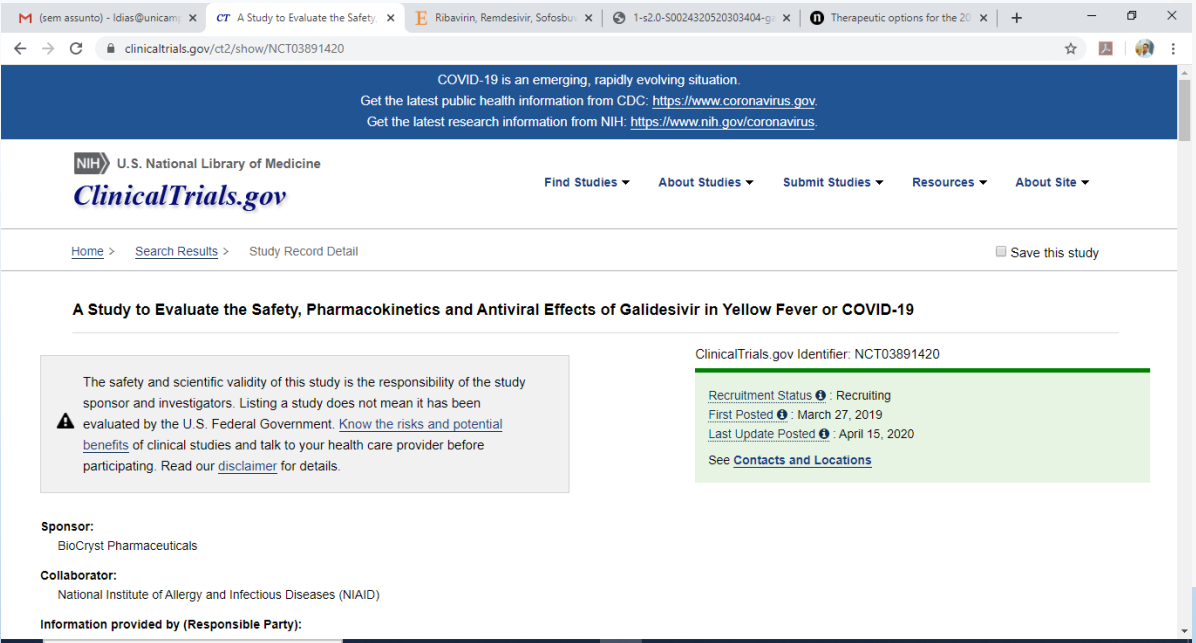


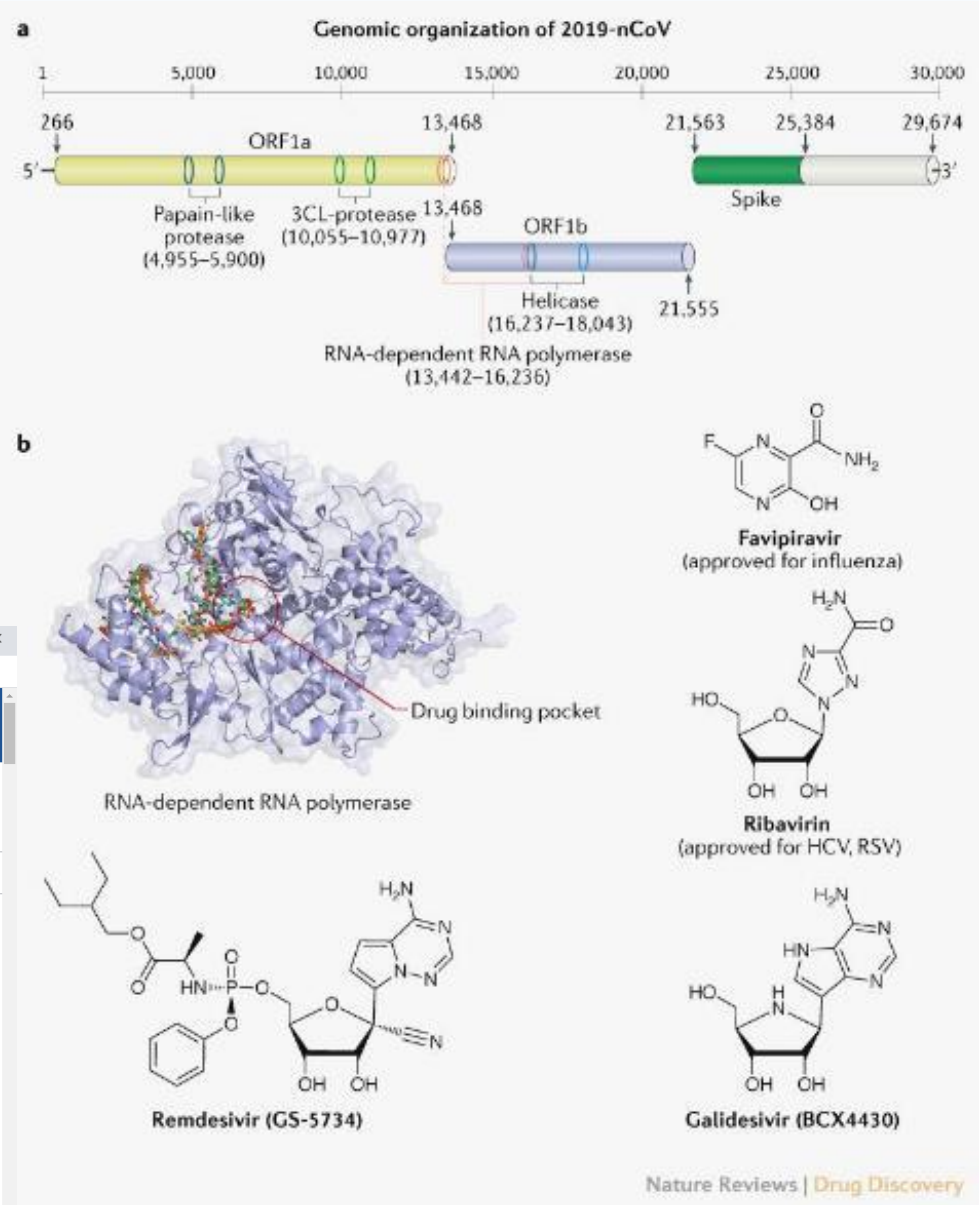
GALIDESIVIR

UNICAMP

Antiviral da fabricante Biocryst Pharma mostrou ampla atividade contra diversos patógenos, incluindo o coronavírus.

Sua atuação inibe o processo de reprodução do vírus, e, por isso, já foi usado, com sucesso, em pacientes com ebola, zika e febre amarela.





https://www.nature.com/articles/d41573-020-00016-0

Cell Research

www.nature.com/cr
www.cell-research.com

LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0

Dear Editor,

In December 2019, a novel pneumonia caused by a previously unknown pathogen emerged in Wuhan, a city of 11 million people in central China. The initial cases were linked to exposures in a seafood market in Wuhan.[1] As of January 27, 2020, the Chinese authorities reported 2835 confirmed cases in mainland China, including 81 deaths. Additionally, 19 confirmed cases were identified in Hong Kong, Macao and Taiwan, and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. The pathogen was soon identified as a novel coronavirus (2019-nCoV), which is closely related to sever acute respiratory syndrome CoV (SARS-CoV).[2] Currently, there is no specific treatment against the new virus. Therefore, identifying effective antiviral agents to combat the disease is urgently needed.

An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The 2019-nCoV belongs to *Betacoronavirus* which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial.[3] In this study, we evaluated the antiviral efficiency of five FAD-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro.

Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoVs. Firstly, the cytotoxicity of the candidate compounds in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019[2] at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. DMSO was used in the controls. Efficacies were evaluated by quantification of viral copy numbers in the cell supernatant via quantitative real-time RT-PCR (qRT-PCR) and confirmed with visualization of virus nucleoprotein (NP) expression through immunofluorescence microscopy at 48 h post infection (p.i.) (cytopathic effect was not obvious at this time point of infection). Among the seven tested drugs, high concentrations of three nucleoside analogs including ribavirin (half-maximal effective concentration (EC_{50}) = 109.50 μM, half-cytotoxic concentration (CC_{50}) > 400 μM, selectivity index (SI) > 3.65), penciclovir (EC_{50} = 95.96 μM, CC_{50} > 400 μM, SI > 4.17) and favipiravir (EC_{50} = 61.88 μM, CC_{50} > 400 μM, SI > 6.46) were required to reduce the viral infection (Fig. 1a and Supplementary information, Fig. S1). However, favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge, although its EC_{50} value in Vero E6 cells was as high as 67 μM,[4] suggesting further in vivo studies are recommended to evaluate this antiviral nucleoside. Nafamostat, a potent inhibitor of MERS-CoV, which prevents membrane fusion, was inhibitive against the 2019-nCoV infection (EC_{50} = 22.50 μM, CC_{50} > 100 μM, SI > 4.44). Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited the 2019-nCoV at a low-micromolar concentration (EC_{50} = 2.12 μM; CC_{50} > 35.53 μM; SI > 16.76). Further in vivo evaluation of this drug against 2019-nCoV infection is recommended. Notably, two compounds remdesivir (EC_{50} = 0.77 μM; CC_{50} > 100 μM; SI > 129.87) and chloroquine (EC_{50} = 1.13 μM; CC_{50} > 100 μM, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high SI (Fig. 1a, b).

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV[5]) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection.[6] Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination.[7] Our time-of-addition assay showed remdesivir functioned at a stage post virus entry (Fig. 1c, d), which is in agreement with its putative antiviral mechanism as a nucleotide analogue. Warren et al. showed that in NHP model, intravenous administration of 10 mg/kg dose of remdesivir resulted in concomitant persistent levels of its active form in the blood (10 μM) and conferred 100% protection against Ebola virus infection.[7] Our data showed that EC_{90} value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76 μM, suggesting its working concentration is likely to be achieved in NHP. Our preliminary data (Supplementary information, Fig. S2) showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV.[2]

Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug.[8,9] Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[10] Our time-of-addition assay demonstrated that chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV infection in Vero E6 cells (Fig. 1c, d). Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration. The EC_{90} value of chloroquine against the 2019-nCoV in Vero

Received: 25 January 2020 Accepted: 28 January 2020
Published online: 4 February 2020

REMDESIVIR

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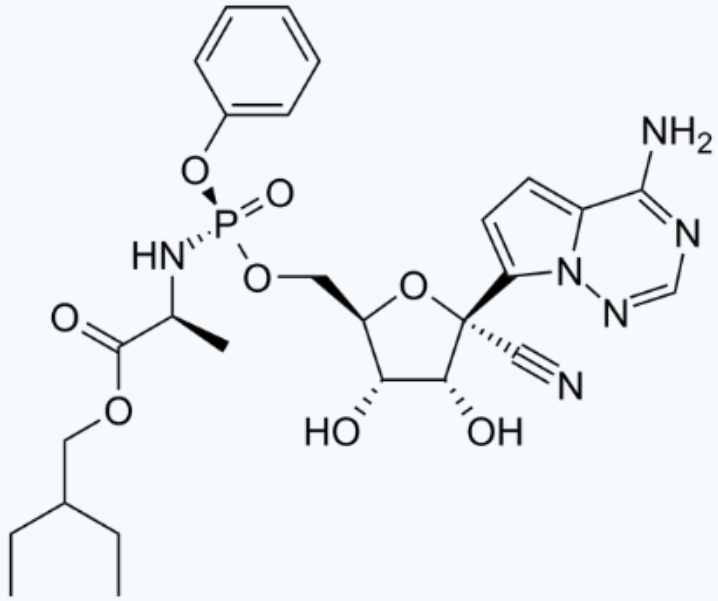

Síntese: *J. Med. Chem.* **2017**, *60*, 1648
~1000 análogos de nucleosídeos

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

ABSTRACT

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brainard at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404, or at diana.brainard@gilead.com.

This article was published on April 10, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2007016

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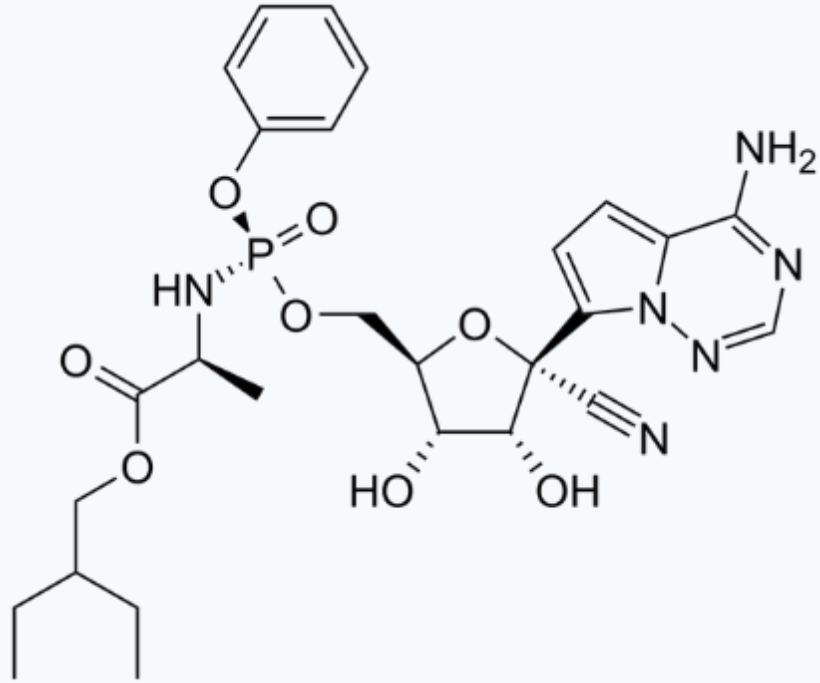

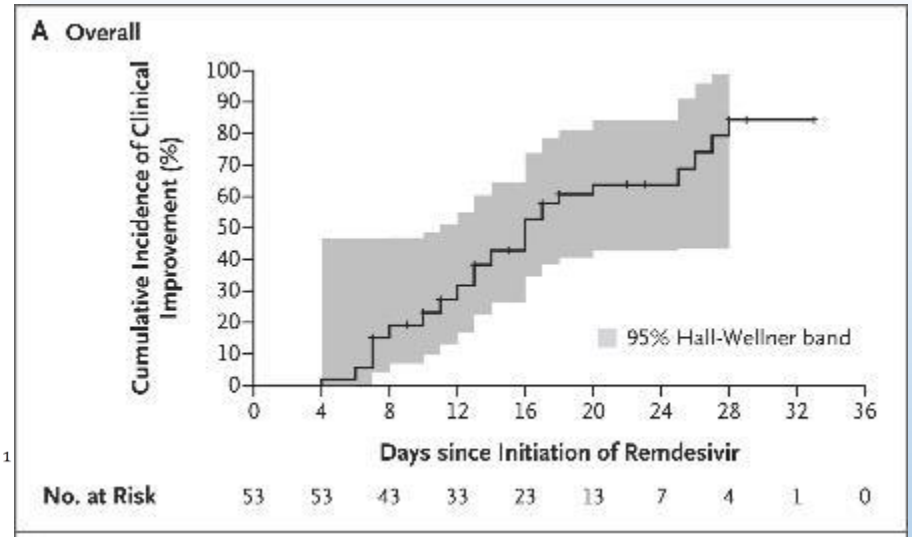

REMDESIVIR

O artigo descreve resultados de 53 pacientes (usando Remdesivir), com COVID-19 confirmada por PCR e que estavam hospitalizados respirando voluntariamente ou com necessidade de suporte de oxigênio.

Dos 53 pacientes, 40 (75%) receberam o esquema completo de dez dias de Remdesivir, 10 (19%) receberam de cinco a nove dias de tratamento e três (6%) receberam menos de cinco dias de tratamento. Pacientes dos Estados Unidos, Japão, Itália, Áustria, França, Alemanha, Holanda, Espanha e Canadá.

A maioria era homem (75%) e a média de idade foi de 64 anos, variando de 23 a 82 anos.

A mortalidade geral foi de 13%, comparado com 22% de mortalidade observada no estudo que avaliou o uso de Lopinavir/Ritonavir, além de melhora em relação à necessidade de suporte de oxigênio em 68% dos pacientes.

Mas há fragilidades do estudo: o número pequeno de pacientes, a ausência de um grupo controle comprometem a análise e generalização dos resultados.

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https://www.statnews.com/2020/04/16/early-peek-at-data-on-gilead-coronavirus-drug-suggests-patients-are-responding-to-treatment/

Dados preliminares de outros dois ensaios clínicos nos EUA usando o Remdesivir para tratar pacientes com com doenças moderadas e o outro em pacientes com doenças graves, são encorajadores.

A Universidade de Chicago é um dos 152 locais que conduzem experimentos da Gilead, com 2.400 pacientes com sintomas graves de COVID-19.

Em carta aberta à Gilead Sciences, empresa de biofarmacologia baseada na Califórnia, mais de 150 organizações sociais e ativistas do mundo todo pedem que a empresa abra mão de reivindicar direitos exclusivos sobre o medicamento Remdesivir.
A iniciativa foi da fundação Médicos Sem Fronteiras.

A Gilead pode reivindicar exclusividade de produção e marketing com base nas patentes que possui em mais de 70 países. Segundo a carta aberta, o monopólio coloca em risco a acessibilidade ao tratamento da COVID-19 para milhões de pessoas em todo o mundo.

(sem assunto) - ldias@unicamp.b | PDB 7bv2 structure summary ‹ Pr

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PDBe › 7bv2

The nsp12-nsp7-nsp8 complex bound to the template-primer RNA and triphosphate form of Remdesivir(RTP)

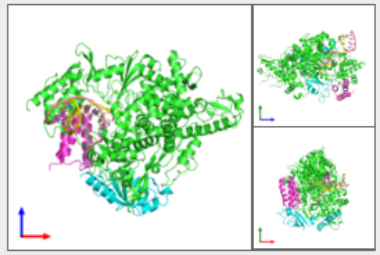
Source organism: *Wuhan seafood market pneumonia virus*

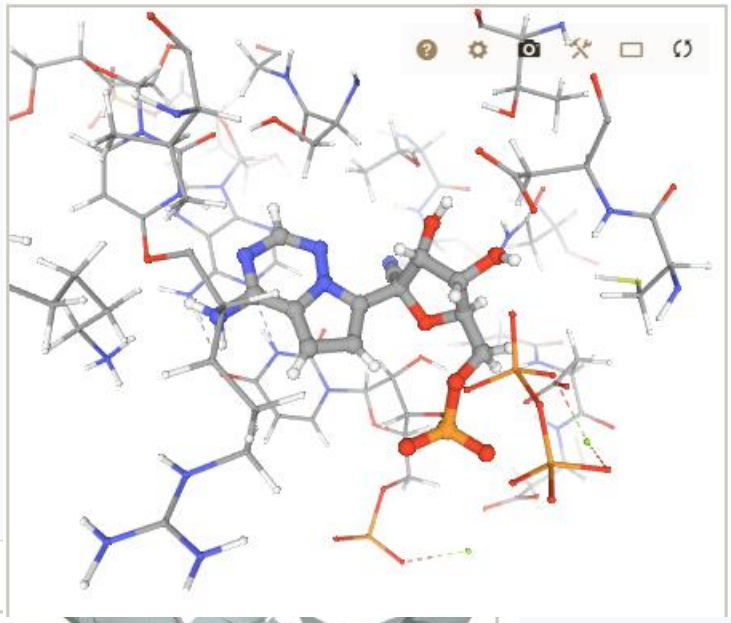
Entry authors: Yin W, Mao C, Luan X, Shen D, Shen Q, Su H, Wang X, Zhou F, Zhao W, Gao M, Chang S, Xie YC, Tian G, Jiang HW, Tao SC, Shen J, Jiang Y, Jiang H, Xu Y, Zhang S, Zhang Y, Xu HE

Related structures: EMD-30210

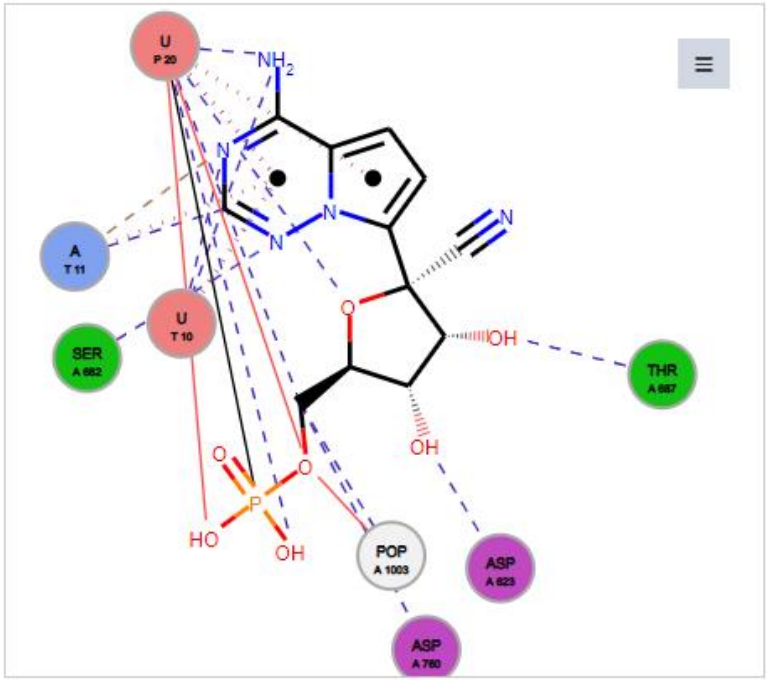
Electron Microscopy
2,5Å resolution

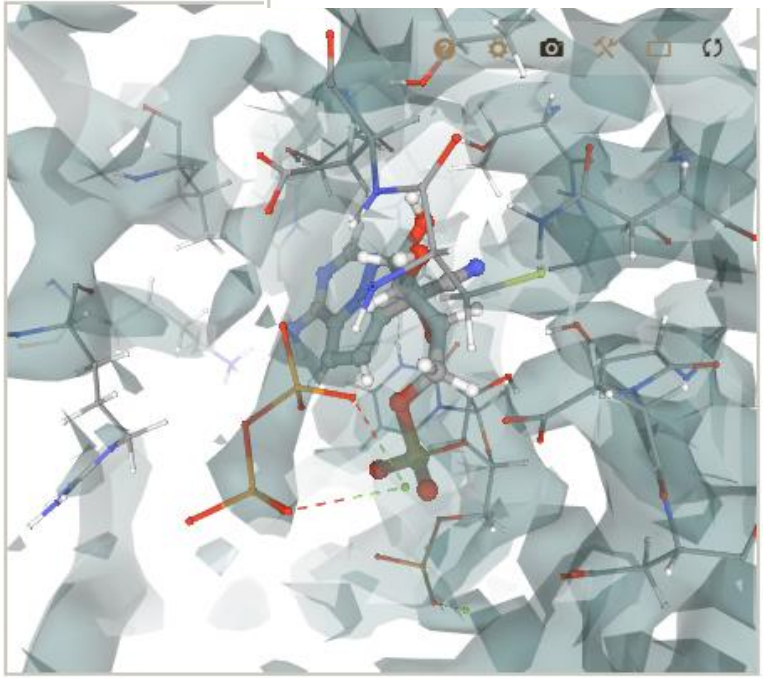
Released: 22 Apr 2020





F86 101 bound to chain P





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CENTRAL DE CONTEÚDO

Apresentações

MCTIC anuncia testes clínicos em pacientes com remédio contra o coronavírus

Medicamento reduziu em 94% a carga viral em ensaios com células e próximo passo são os testes clínicos com 500 pacientes. Resultado deve ser concluído em maio

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GOVERNO TESTA MEDICAMENTO "SECRETO" CONTRA A COVID-19

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Foram testados 2 mil medicamentos com o objetivo de identificar fármacos compostos por moléculas capazes de inibir proteínas fundamentais para a replicação viral. Com uso de alta tecnologia como biologia molecular e estrutural, computação científica, quimioinformática e inteligência artificial, os pesquisadores identificaram seis moléculas promissoras que seguiram para teste *in vitro* com células infectadas com o SARS-CoV-2 (Laboratório Nível 3 IB/Unicamp). Desses seis remédios pesquisados, os cientistas do CNPEM/MCTIC descobriram que dois reduziram significativamente a replicação viral em células. **O remédio mais promissor apresentou 94% de eficácia em ensaios com as células infectadas.**

Na terça-feira, 14 de abril, o ensaio clínico financiado pelo MCTIC obteve a autorização da Comissão Nacional de Ética em Pesquisa (CONEP) para realizar a última etapa dos testes: ***OS ENSAIOS CLÍNICOS EM PACIENTES INFECTADOS COM O NOVO CORONAVÍRUS (SARS-CoV-2).*** Já nas próximas semanas começam os testes com um grupo de 500 pacientes, que serão realizados por sete hospitais das Forças Armadas, localizados no Rio de Janeiro (5), São Paulo (1) e Brasília (1).

GOVERNO TESTA MEDICAMENTO "SECRETO" CONTRA A COVID-19

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pfarma.com.br/coronavirus/5447-nitazoxanida-controlado.html

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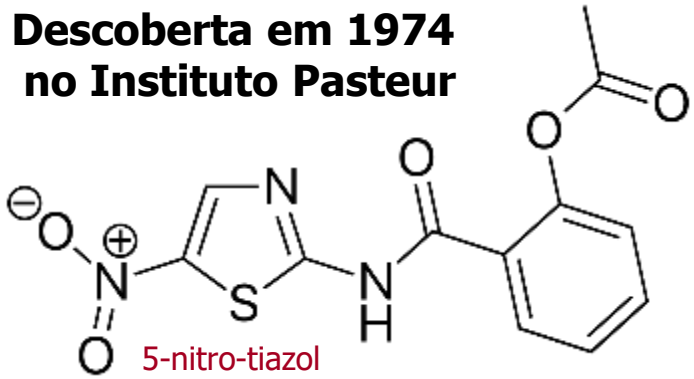

5-nitro-tiazol

Journal of Infection and Public Health (2016) 9, 227—230

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http://www.elsevier.com/locate/jiph

Testado antes para outros coronavírus, sem sucesso

Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus

Jean-François Rossignol*

Romark Laboratories, L.C., Tampa, FL, United States

Received 14 March 2016; received in revised form 21 March 2016; accepted 2 April 2016

KEYWORDS
Nitazoxanide;
Coronavirus;
MERS-CoV;
Treatment

Summary Nitazoxanide is a broad-spectrum antiviral agent undergoing clinical development for treatment of influenza and other viral respiratory infections. Nitazoxanide exhibits *in vitro* activity against Middle East respiratory syndrome coronavirus (MERS-CoV) and other coronaviruses, inhibiting expression of the viral N protein. Nitazoxanide also suppresses production of pro-inflammatory cytokines in peripheral blood mononuclear cells and suppresses interleukin 6 production in mice. Having been used extensively in clinical trials and in post-marketing experience, nitazoxanide is an attractive drug candidate for treatment of Middle East respiratory syndrome. Future research should include *in vitro* mechanism studies, animal models of MERS-CoV infection, clinical trials, including dose-ranging trials, and evaluation of combination therapy with other potential MERS-CoV antivirals.

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CONTROLE ESPECIAL

Nitazoxanida: orientação aos pacientes e farmácias

Com o novo enquadramento, as farmácias e drogarias devem registrar todas as entradas e saídas do medicamento e seu estoque, além dos dados dos consumidores.

Por: Ascom/Anvisa

Publicado: 16/04/2020 14:36
Última Modificação: 16/04/2020 15:44

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Toda prescrição de medicamento à base de nitazoxanida agora precisa ser feita em receita especial de duas vias. A determinação está na Resolução da Diretoria Colegiada (RDC) 372/2020 da Anvisa, publicada nesta

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A nitazoxanida, citada por Pontes, é testada em quatro países: Egito, México e EUA também avaliam nitazoxanida para tratar Covid-19

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clinicaltrials.gov/ct2/show/NCT04341493

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COVID-19 is an emerging, rapidly evolving situation.
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Get the latest research information from NIH: https://www.nih.gov/coronavirus.

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Hydroxychloroquine vs Nitazoxanide in Patients With COVID-19

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ClinicalTrials.gov Identifier: NCT04341493

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Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)
A Review

James M. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; James B. Cutrell, MD

IMPORTANCE The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. Given the rapid pace of scientific discovery and clinical data generated by the large number of people rapidly infected by SARS-CoV-2, clinicians need accurate evidence regarding effective medical treatments for this infection.

OBSERVATIONS No proven effective therapies for this virus currently exist. The rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The most promising therapy is remdesivir. Remdesivir has potent in vitro activity against SARS-CoV-2, but it is not US Food and Drug Administration approved and currently is being tested in ongoing randomized trials. Oseltamivir has not been shown to have efficacy, and corticosteroids are currently not recommended. Current clinical evidence does not support stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19.

CONCLUSIONS AND RELEVANCE The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.

JAMA. doi:10.1001/jama.2020.6019
Published online April 13, 2020.

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Assessment of Evidence for COVID-19-Related Treatments: Updated 4/22/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use. Public access to AHFS Drug Information® (https://www.ahfscdi.com/login) is available for the next 60 days with the username "ahfs@ashp.org" and password "covid-19." ASHP's patient medication information is available at http://www.safemedication.com/.

Select entries were updated on 4/22/2020; these can be identified by the date that appears in the Drug(s) column.

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https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx

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https://science.sciencemag.org/content/sci/367/6485/1412.full.pdf

IN DEPTH

Medical staff treat a patient with the novel coronavirus this month in Wuhan, China.

INFECTIOUS DISEASES

Race to find COVID-19 treatments accelerates

WHO launches megatrial to test repurposed drugs and experimental drug candidates

By **Kai Kupferschmidt** and **Jon Cohen**

With cases of the new coronavirus disease 2019 (COVID-19) climbing steeply everywhere from Madrid to Manhattan, overwhelming one hospital after another and pushing the global death toll past 17,000, the sprint to find treatments has dramatically accelerated. Drugs that stop the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could save the lives of severely ill patients, protect health care workers and others at high risk of infection, and reduce the time patients spend in hospital beds.

The World Health Organization (WHO) last week announced a major study to compare treatment strategies in a streamlined clinical trial design that doctors around the world can join. Other trials are also underway; all told, at least 12 potential COVID-19 treatments are being tested, including drugs already in use for HIV and malaria, experimental compounds that work against an array of viruses in animal experiments, and antibody-rich plasma from people who have recovered from COVID-19. More than one strategy may prove its worth, and effective treatments may work at different stages of infection, says Thomas Gallagher, a coronavirus researcher at Loyola University Chicago's Health Sciences Campus. "The big challenge may be at the clinical end determining when to use the drugs."

Researchers want to avoid repeating the mistakes of the 2014–16 West African Ebola epidemic, in which willy-nilly experiments proliferated but randomized clinical trials were set up so late that many ended up not recruiting enough patients. "The lesson is you start trials now," says Arthur Caplan, a bioethicist at New York University's Langone Medical Center. "Make it a part of what you're doing so that you can move rapidly to have the most efficacious interventions come to the front."

To that end, WHO on 20 March announced the launch of SOLIDARITY, an unprecedented, coordinated push to collect robust scientific data rapidly during a pandemic. The study, which could include many thousands of patients in dozens of countries, has emphasized simplicity so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate. WHO's website will randomize patients to local standard care or one of the four drug regimens, using only ones available at the patient's hospital. Physicians will simply record the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation. "That's all," says Ana Maria Henao Restrepo, a medical officer at WHO's Emergencies Programme.

The design is not blinded: Patients will know they received a drug candidate, and that could cause a placebo effect, Henao Restrepo concedes. But it is in the interest of speed, she says. "We are doing this in record time." The agency hopes to start to enroll patients this week.

Rather than taking years to develop and test compounds from scratch, WHO and others want to repurpose drugs that are already approved for other diseases and have acceptable safety profiles. They're also looking at experimental drugs that have performed well in animal studies against the other two deadly coronaviruses, which cause SARS and Middle East respiratory syndrome (MERS). And they are focusing on compounds plentiful enough to treat a substantial number of patients.

For its study, WHO chose an experimental antiviral called remdesivir; the malaria medication chloroquine (or its chemical cousin hydroxychloroquine); a combination of the HIV drugs lopinavir and ritonavir; and that combination plus interferon-beta, an immune system messenger that can help cripple viruses. The treatments would stop the virus by different mechanisms, but each has drawbacks.

Remdesivir, developed by Gilead Sciences to combat Ebola and related viruses, shuts down viral replication by inhibiting a key viral enzyme, the RNA polymerase. It didn't help patients with Ebola in a test during the 2019 outbreak in the Democratic Republic of the Congo. But in 2017, researchers showed in test tube and animal studies that the drug can inhibit the SARS and MERS viruses.

The drug, which is given intravenously, has been used in hundreds of COVID-19 patients in the United States and Europe under what's known as compassionate use, which required Gilead to review patient records; some doctors have reported anecdotal evidence of benefit, but no hard data. Gilead says it is now starting to supply remdesivir under a simpler "expanded use" designation. Five other clinical trials underway in China and the United States are testing it and may have preliminary results soon. Of the drugs in the SOLIDARITY trial, "remdesivir has the best potential," says Shibo

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TERAPIA DE PLASMA CONVALESCENTE

UNICAMP

O plasma sanguíneo corresponde a cerca de 55% do sangue.
Apresenta cor amarelada e é composto por cerca de 90% de água + proteínas, sais, lipídios, hormônios e vitaminas.

A FDA, agência de medicamentos norte-americana, aprovou testes clínicos envolvendo a retirada de plasma sanguíneo de pacientes em recuperação do coronavírus, com potencial de diminuir a gravidade ou a duração da doença causada pelo vírus.

O tratamento envolve a retirada de plasma sanguíneo de um paciente que já teria desenvolvido imunidade à doença. Em seguida, o plasma seria injetado em pacientes graves, para que o anticorpo ataque o vírus, reduzindo a carga viral.

Leucócitos (glóbulos brancos) contém neutrófilos, linfócitos e macrófagos
Linfócitos são células de defesa, anticorpos, que são proteínas antivirais

Há riscos? Sim, riscos de transmissão de doenças.

Um consórcio formado pelo Hospital Israelita Albert Einstein, o Hospital Sírio-Libanês e a Universidade de São Paulo (USP) começará a realizar testes clínicos para uso do sangue de pacientes que já se recuperaram do coronavírus em doentes graves da doença.

A OMS não tem certeza sobre se a presença de anticorpos no sangue fornece proteção total contra a reinfecção pelo coronavírus, porcentagem muito pequena da população tenha soroconvertido (para produzir anticorpos).

VACINAS

As bases das vacinas em teste são diferenciadas.

Em um dos estudos, a vacina de mRNA é constituída por uma fita de ácido nucleico (RNA) que contém uma mensagem, ou seja, a informação para uma proteína do coronavírus SARS-COV-2, chamada Spike.

Um outro tipo de vacina envolve a aplicação de adenovírus, um vírus atenuado que não causa doença em humanos.

Uma das vacinas se baseia em um adenovírus modificado expressando a proteína Spike, o que se chama de quimera viral (híbrido de dois vírus).

O adenovírus usado pode ser humano ou de chimpanzés.

VACINAS

O desenvolvimento de uma vacina pode levar no mínimo mais um ou dois anos, talvez mais, já que é preciso garantir também que ela funcione e não tenha o efeito contrário, de nos deixar mais vulneráveis ao vírus.

Vacina de RNA - Instituto de Pesquisa em Saúde Kaiser Permanente, em Seattle (EUA): Primeira vacina contra a Covid-19 a ser testada em humanos, a imunização se baseia em trechos de RNA que compõem o material genético do vírus.

Vacina chinesa com adenovírus modificado: Criada pela empresa farmacêutica CanSino, foi a primeira a alcançar a fase 2 dos testes clínicos, recrutando 500 voluntários no dia 15 de abril de 2020 e deve durar cerca de um ano. Usa abordagem de patógeno modificado, do grupo dos adenovírus, como vetor.

Vacina Inovio Pharmaceuticals (EUA) com DNA: A abordagem começou a ser testada na fase 1 em 6 de abril de 2020. O método tem semelhanças com a vacina de RNA, com a diferença de que o genoma do vírus, na parte correspondente ao código da proteína S, foi adaptado para uma molécula de DNA.

Brasil O imunologista Jorge Kalil, diretor do laboratório de imunologia do Instituto do Coração (Incor), em São Paulo, lidera uma pesquisa financiada pela Fapesp para desenvolver uma vacina contra o novo coronavírus. Síntese em laboratório de uma parte de uma proteína do coronavírus.

Suíça: Cientistas suíços esperam ter vacina contra o coronavírus em outubro, disse o chefe de Imunologia do Hospital Universitário de Berna.

TEMPO PARA DESENVOLVIMENTO DE VACINAS

A vacina da dengue começou a ser desenvolvida pelo Instituto Butantã em 2009.
Em 2013, foi feito o primeiro teste em seres humanos.

Mais de 17 mil pessoas de 16 centros de todo o país foram vacinadas em 2016, um terço delas com placebo e estão sendo monitoradas. O recrutamento aconteceu entre 2016 e 2019.

Essas pessoas serão monitoradas por 5 anos, até 2021. Depois, o estudo será submetido à Agência Nacional de Vigilância Sanitária (Anvisa) solicitando registro. Com ele, a vacina começa a ser produzida em larga escala e ficará disponível para comercialização.

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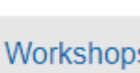

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