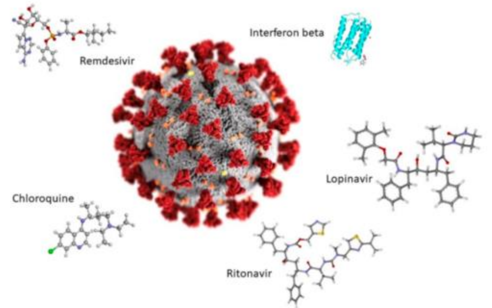


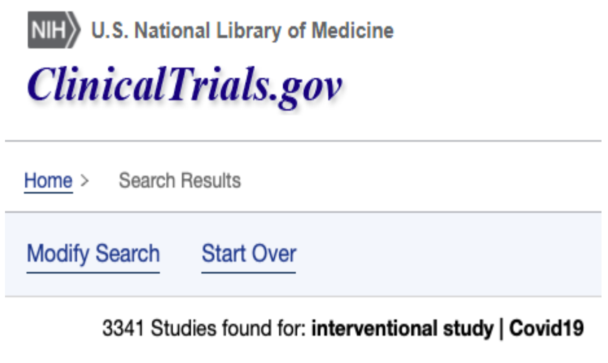
LIỆU PHÁP KHÁNG VIRUS CHO BỆNH NHÂN SARS-COV-2

BSCK1. THÁI MINH CẢNH

BỘ MÔN HỒI SỨC - CẤP CỨU - CHỐNG ĐỘC

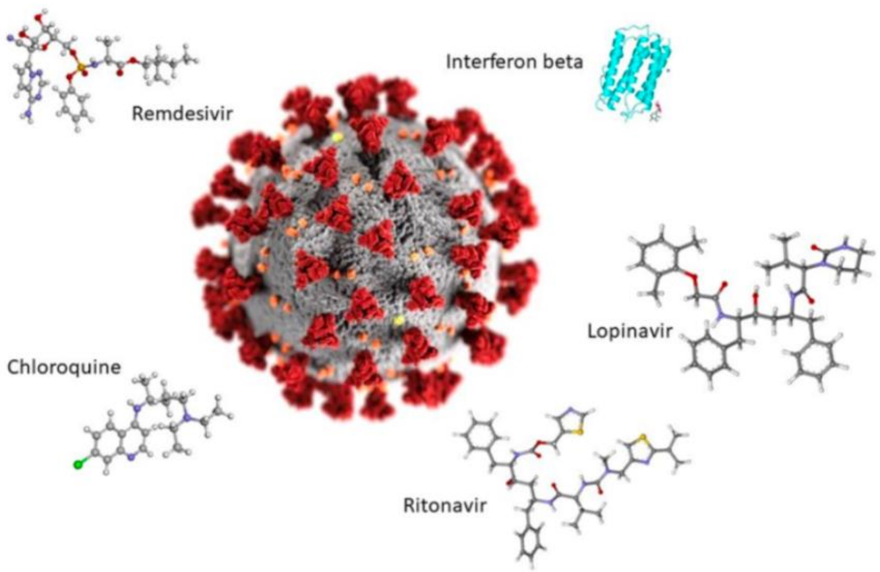
ĐẠI HỌC Y DƯỢC TP. HỒ CHÍ MINH

TỔNG QUAN



Nguồn: https://clinicaltrials.gov (6/2021)

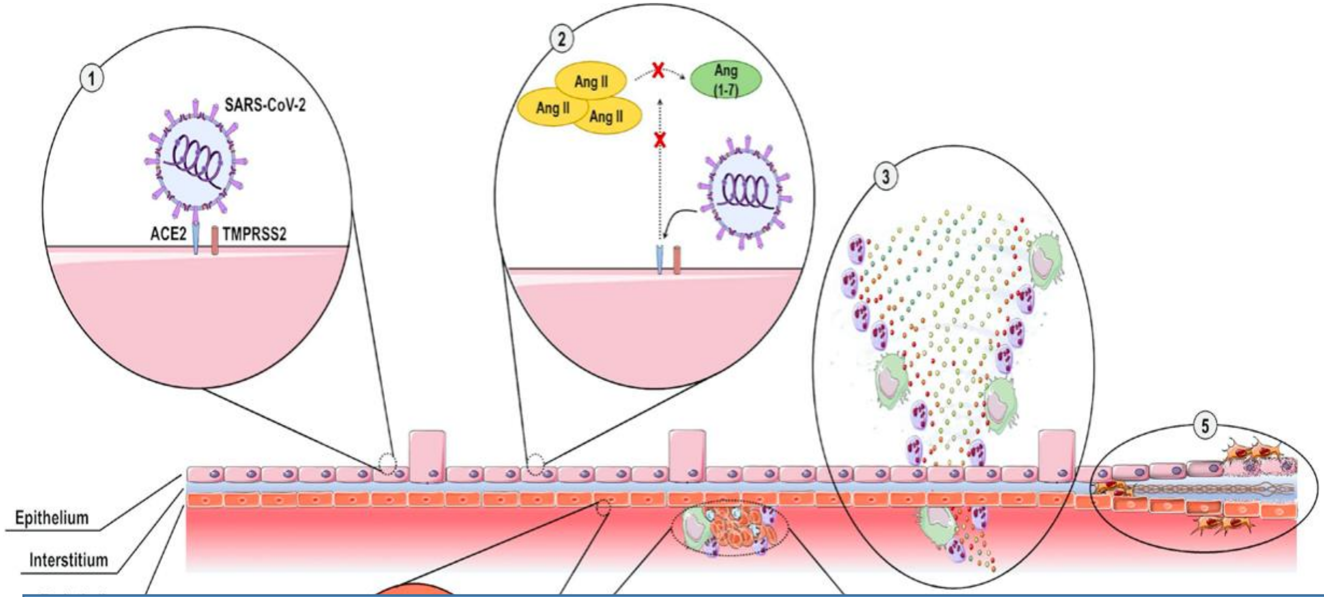
TỔNG QUAN



- Cơ chế bệnh sinh phức tạp.
- **Chưa có thuốc điều trị đặc hiệu.**
- Tình trạng đột biến các chủng virus mới siêu lây lan.
- Tỷ lệ dân số tiêm ngừa vaccine còn thấp.
- Các thuốc đang được nghiên cứu thử nghiệm lâm sàng hiện tại dựa vào hiệu quả rút ra từ các nghiên cứu trước đây với đại dịch SARS (2002-2004), Ebola (2014).

NHỮNG THUỐC CŨ TRONG THẾ GIỚI COVID-19 MỚI

CƠ CHẾ BỆNH SINH



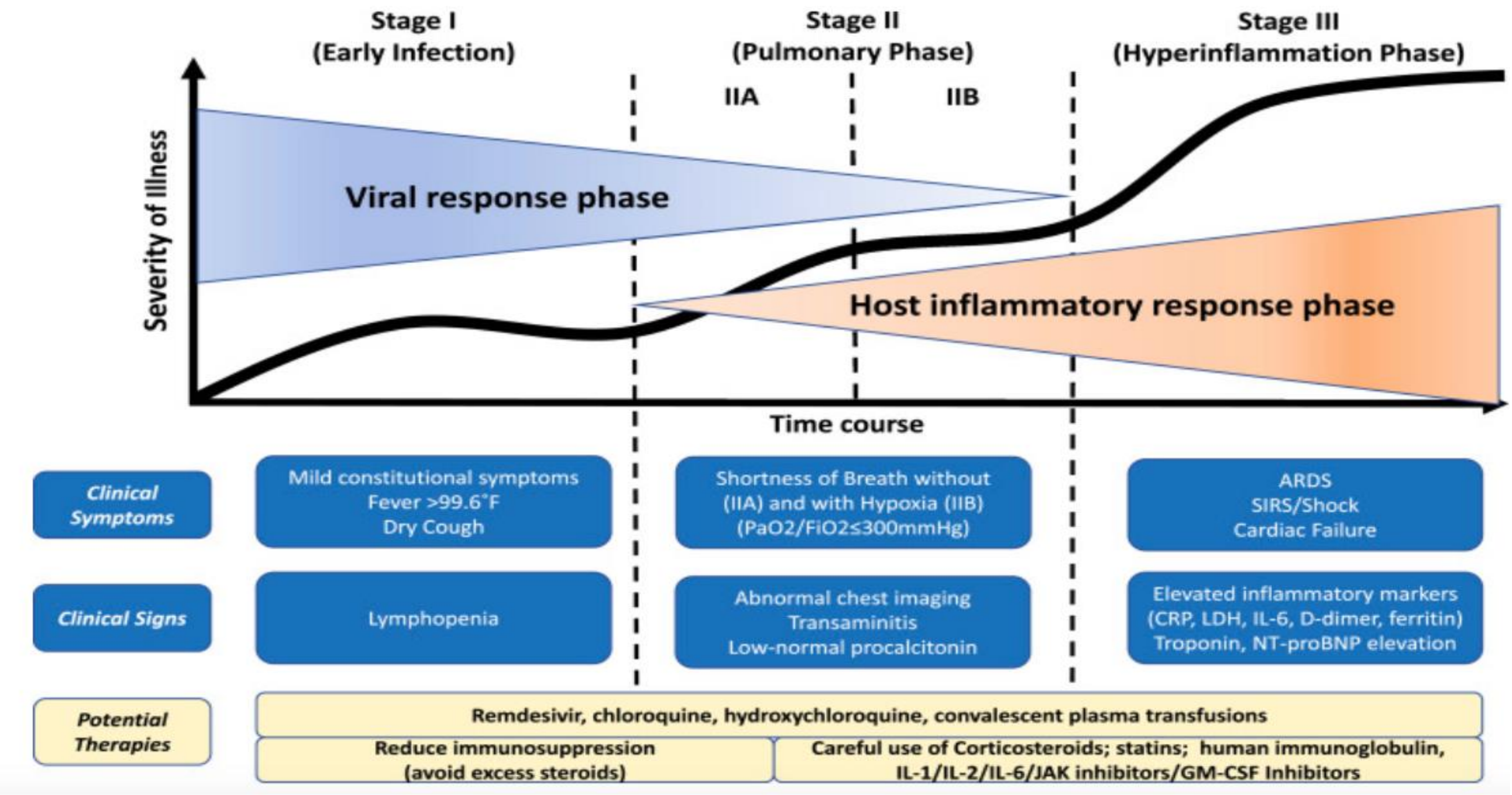
1. Tổn thương do tác động trực tiếp của virus → *Thuốc kháng virus*
2. Tổn thương tiến triển do đáp ứng điều hòa của cơ thể bị rối loạn → *Tác nhân điều hòa miễn dịch*

5 cơ chế bệnh sinh chính trong diễn tiến của virus SARS-CoV-2

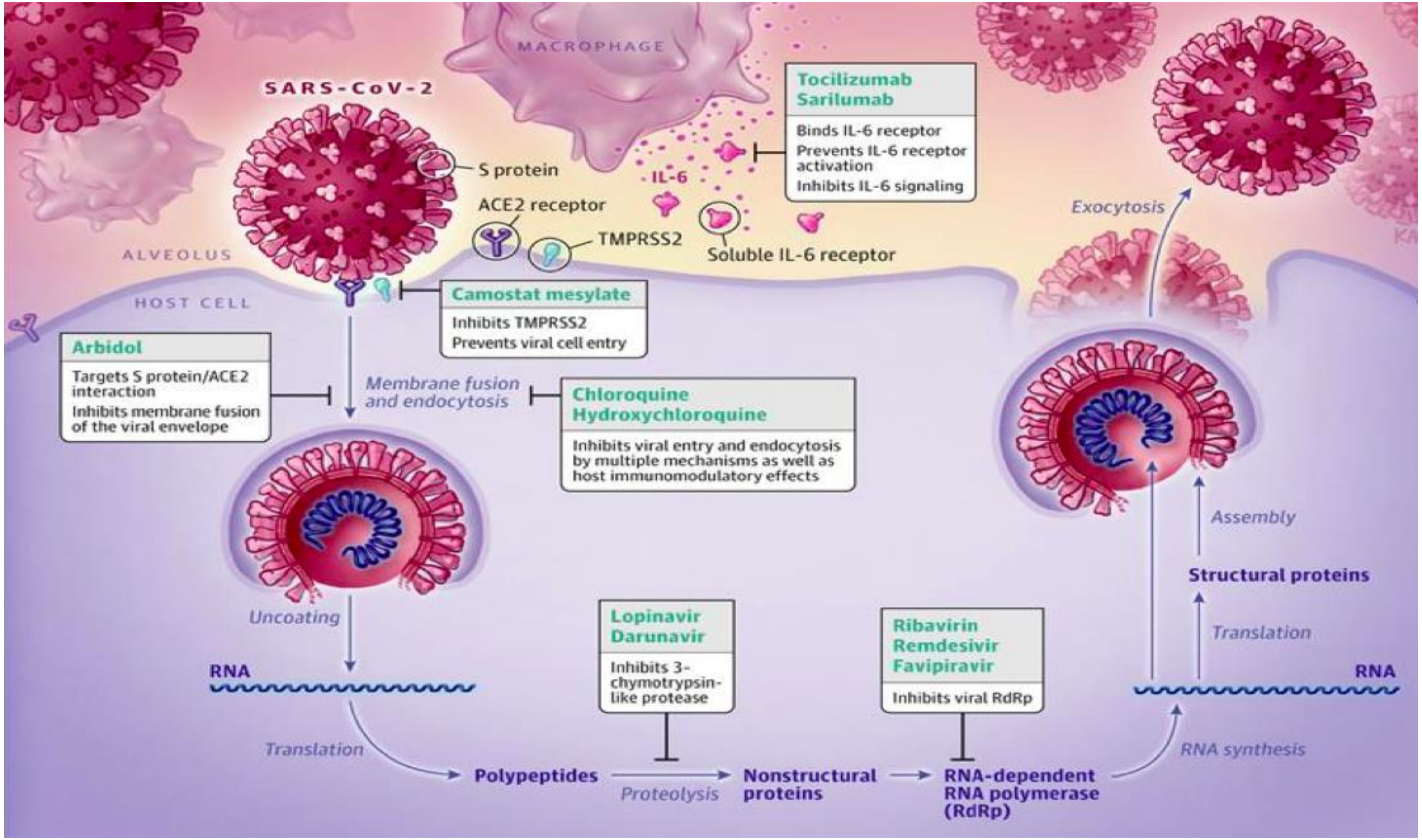
1. Protein S được mồi bởi TMPRSS2 và tương tác với ACE2 gây độc TB.
2. “Downregulation” biểu hiện ACE2 → ức chế quá trình phân tách Ang II → rối loạn điều hòa hệ RAA.
3. Rối loạn đáp ứng miễn dịch.
4. Tổn thương lớp nội mô → tái huy động TB trợ viêm, hoạt hóa dòng thác đông máu.
5. Phá hủy mô quá mức → dày mô kẽ, tăng quá trình xơ hóa.

Nguồn: Lopes-Pacheco M (2021) . Pathogenesis of multiple organ injury in COVID-19 and potential therapeutic strategies. *Front Physiol*.

DIỄN TIẾN BỆNH SINH CỦA NHIỄM SARS-COV-2



CÁC ĐÍCH TÁC ĐỘNG CỦA THUỐC KHÁNG VIRUS



Quá trình xâm nhập, sao chép của virus SARS-CoV-2 khi tấn công cơ thể người và các đích tác động của thuốc kháng virus

Nguồn: Sanders (2020). Pharmacologic treatments for coronavirus disease 2019: a review. *JAMA*, 323(18), 1824-1836.

CÁC ĐÍCH TÁC ĐỘNG CỦA THUỐC KHÁNG VIRUS

Ức chế sự xâm nhập của virus

- Ức chế TMPRSS2 (Camostat)
- Ức chế Protein S – ACE2 (Umifenovir)
- Các thuốc khác (HCQ/CQ, Barcitinib, Oseltamivir…)

Ức chế sự tổng hợp RNA của virus

- Ức chế RdRp (Remdesivir, Favipiravir, Ribavirin, Sofosbuvir)
- Ức chế protease (Lopinavir/r)

Điều hòa miễn dịch (Corticosteroid, điều hòa IL-6, Interferon…)

CÁC NHÓM THUỐC ĐANG ĐƯỢC TNLS

Các nhóm thuốc đang được TNLS:

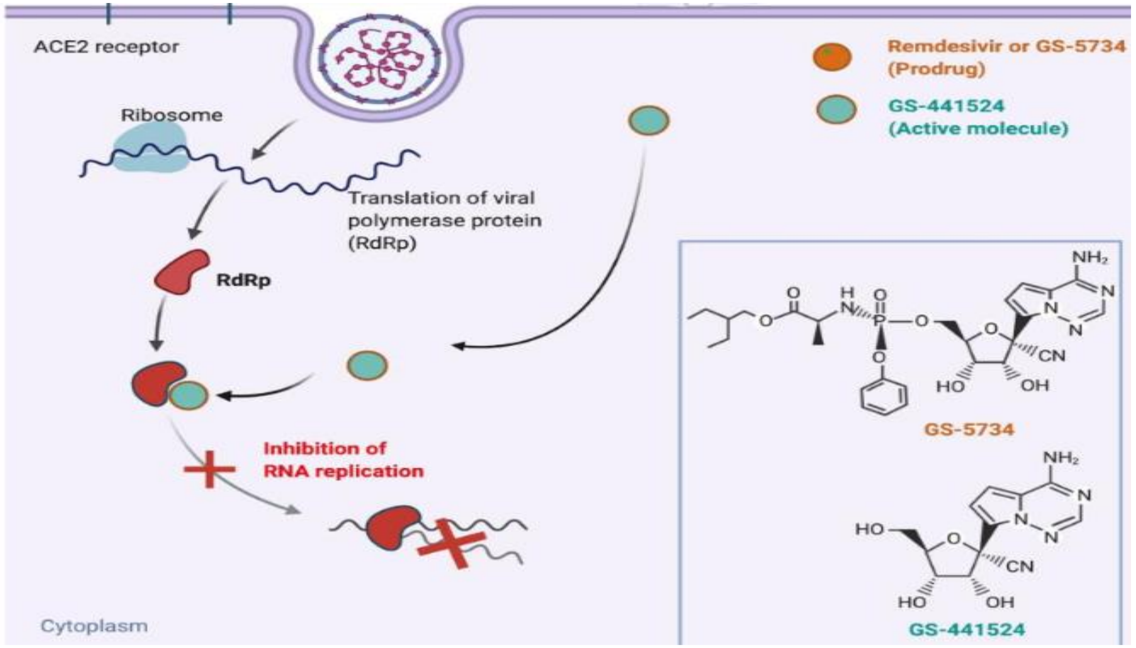
1. **Thuốc kháng virus: Remdesivir, LPV/r, HCQ, Favipiravir…**
2. Điều hòa miễn dịch: Tocilizumab, Sarilumab, Anakinra…
3. Kháng thể: globulin miễn dịch hiệu giá kháng thể cao, huyết tương ở bệnh nhân hồi phục.
4. Thuốc kháng viêm: Dexamethasone, Statins
5. Kháng đông
6. Chất chống xơ hóa: chất ức chế tyrosin kinase

CÁC THUỐC KHÁNG VIRUS ĐƯỢC NGHIÊN CỨU NHIỀU

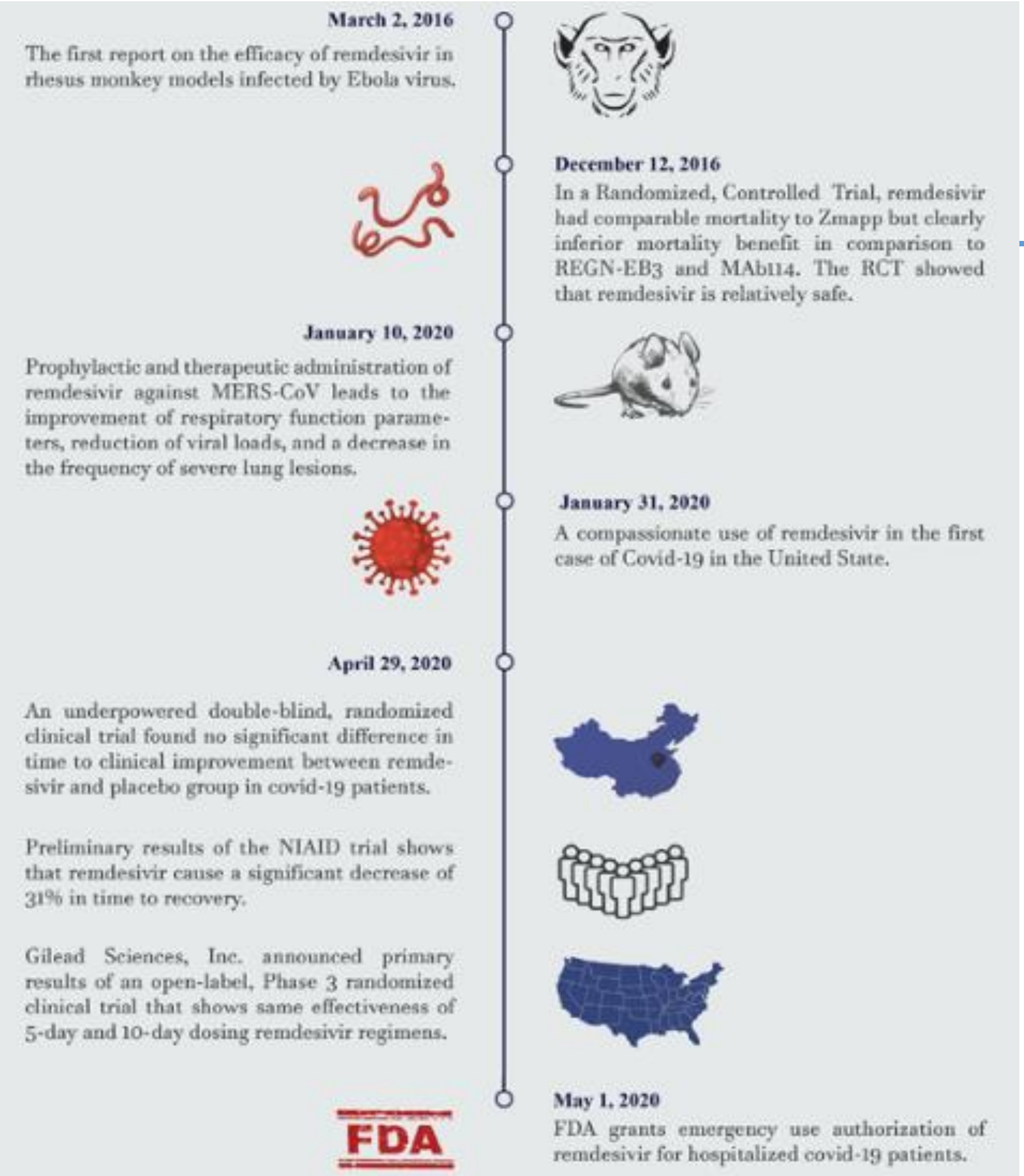
1. **Remdesivir (GS-5734)**
2. **Chloroquine và Hydroxychloroquine**
3. Lopinavir/Ritonavir (LPV/r)
4. Umifenovir (Arbidol)
5. Faripiravir (FPV)

Remdesivir (GS-5734)

RDV, a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including **SARS-CoV-2 in vitro** and inhibits **SARS-CoV-2 replication in animal models**.



Remdesivir and its antiviral activity against COVID-19: A systematic review (2020)



Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

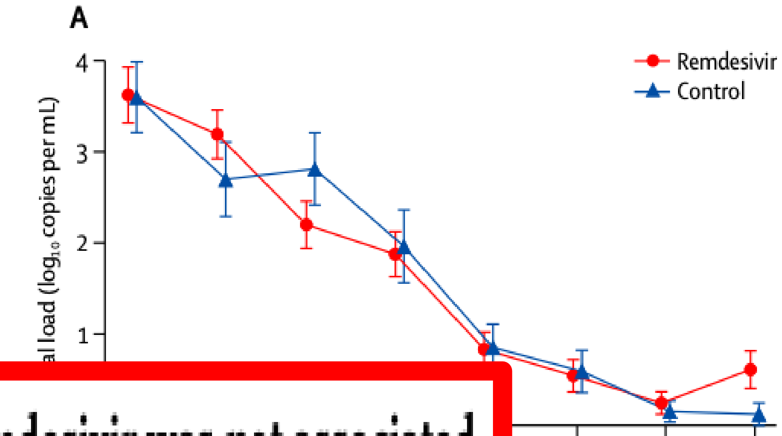
- **P:** 237 BN nhiễm SARS-CoV-2 trong vòng 12 ngày, SpO2 <=94% (khí trời), hình ảnh viêm phổi trên Xquang.
- **I + C:** Chia 2 nhóm (2:1) gồm RDV và placebo trong 10 ngày. Có thể sử dụng các thuốc khác (LPV/r, Interferon, Corticoids).
- **O:** Tử vong 28 ngày, tỷ lệ hồi phục và thời gian thở máy.

Nguồn: ***Lancet* 2020; 395: 1569–78**

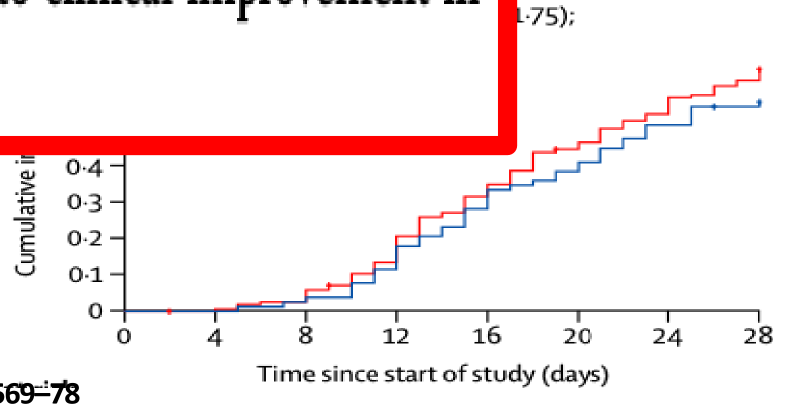
Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (–8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	-3·6% (–16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (–8·2 to 17·4)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	-2·5 (–11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	-2·0 (–6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (–4·0 to 4·0)



Interpretation In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.



Day 1: 200mg RDV (IV)

Day 2-10: 100mg RDV (IV)

Nguồn: *Lancet* 2020; 395: 1569–78

ACTT-1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh,

ACTT-1 randomized 1062 hospitalized patients with COVID-19 and lower respiratory tract infection to receive 10 days of intravenous remdesivir or placebo. The main results were the following:

- The remdesivir group had a shorter median time to recovery than the placebo group: 10 versus 15 days.
- The mortality estimate by day 29 was 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% confidence interval, 0.52–1.03).
- Mortality differences between remdesivir and placebo recipients varied by disease severity. In the subgroup receiving supplemental oxygen at baseline (but not through a high-flow device, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), mortality estimates were 4% with remdesivir and 12.7% with placebo (hazard ratio for death, 0.3; 95% CI, 0.14–0.64).

ACTT-2

	Combination (RDV+Bari)	Control (RDV+placebo)	
Median time to recover	7 days	8 days	RR = 1.16 (95% CI, 1.01 – 1.32) p = 0.03
Median time to recover in NIV/HFNC	10 days	18 days	RR = 1.51 (95% CI, 1.10 – 2.08)
Recovery rate			
NO oxygen			RR = 0.88 (95% CI, 0.63 – 1.23)
Supplemental Oxygen			RR = 1.17 (95% CI, 0.98 – 1.39)
NIV/HFNC			RR = 1.08 (95% CI, 0.59 – 1.97)
Improvement in clinical status at day 15			OR = 1.3 (95% CI, 1.0 - 1.6)
Improvement in clinical status at day 15 at NIV/HFNC			OR = 2.2 (95% CI, 1.4 – 3.6)
Mortality at 28 day	5.1% (3.5 – 7.6%)	7.8% (5.7 – 10.6%)	HR = 0.65 (95% CI, 0.39 – 1.09)
Mortality at 14 day	1.6%	3.0%	HR = 0.54 (95% CI, 0.23 – 1.28)

ACTT-2

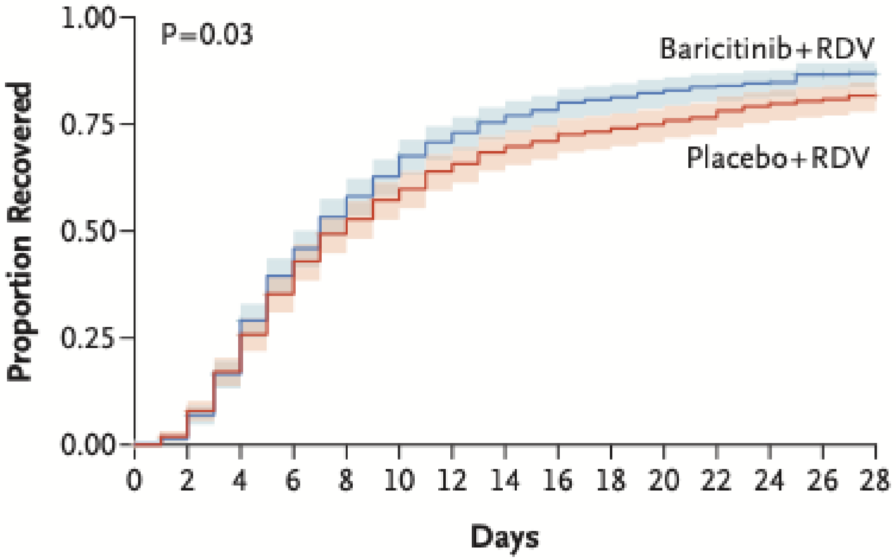
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2021 VOL. 384 NO. 9

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos,

A Overall



CONCLUSIONS

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04401579.)

Nguồn: N Engl J Med 2021;384:795-807

JAMA | Original Investigation

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19
A Randomized Clinical Trial

Christoph D. Spinner, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; Jo
Alex Soriano Viladomiu, MD; Onyema Ogbuagu, MD; Prashant Malhotra, MD; K
Louis Yi Ann Chai, MD; Meta Roestenberg, MD; Owen Tak Yin Tsang, MD; Enos

- **P:** 596 BN nhiễm SARS-CoV-2 mức độ trung bình (SpO2 >94%).
- **I+C:** Chia ngẫu nhiên 3 nhóm (1:1:1) gồm 10 ngày RDV, 5 ngày RDV và nhóm “standard care”.
- **O:** Tình trạng lâm sàng vào ngày 11 dựa trên thang điểm “7-point ordinal scale”.

Nguồn: JAMA. 2020;324(11):1048-1057

Table 2. Clinical Outcomes

Outcomes	10-Day remdesivir (n = 193)	5-Day remdesivir (n = 191)	Standard care (n = 200)
Day 28	174 (90)	171 (90)	166 (83)
Recovery, No. (%)[c]			
Day 5	74 (38)	67 (35)	71 (36)
Day 7	94 (49)	114 (60)	101 (51)
Day 11	132 (68)	141 (74)	128 (64)
Difference in percentage vs standard care at day 11 (95% CI)	4.4 (−5.0 to 13.8)	9.8 (0.3-19.0)	
Day 14	153 (79)	153 (80)	145 (73)
Day 28	178 (92)	175 (92)	170 (85)

CONCLUSIONS AND RELEVANCE Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

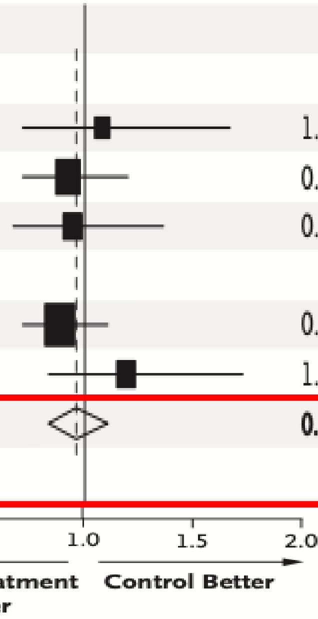
Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

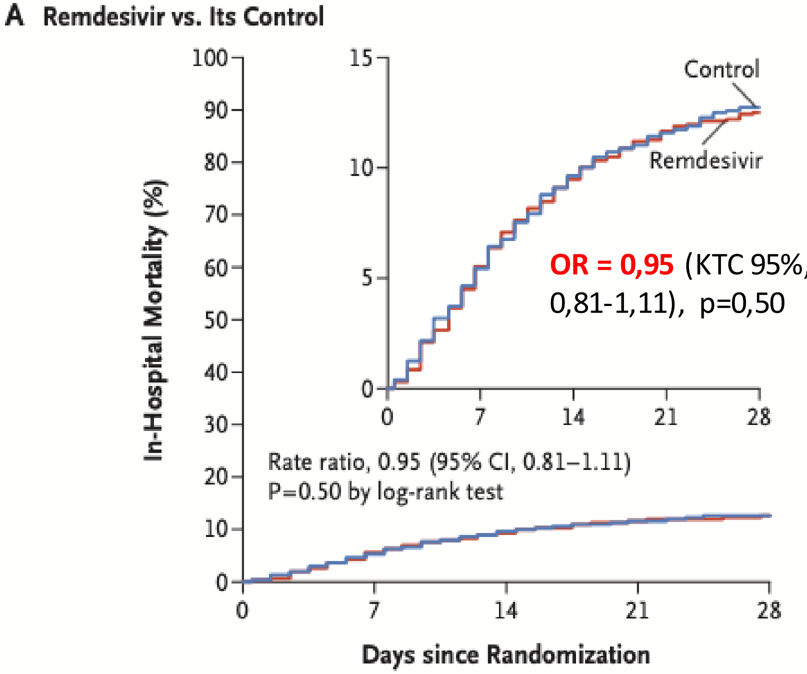
11330 BN từ 30 quốc gia:

- 2750 BN dùng RDV
- 954 BN dùng HCQ
- 1411 BN dùng LPV/r
- 2063 BN dùng interferon (gồm 651 LPV)

Subgroup	Active Treatment	Control	Log-Rank Statistics for No. of Deaths in Active-Treatment Group O−E	Variance	Rate Ratio for Death (99% CI; 95% CI for total)
	no. of deaths reported/no. of patients (%)				
Remdesivir					
Age at entry					
<50 yr	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 (0.67–1.73)
50–69 yr	154/1282 (13.8)	161/1287 (14.2)	−7.6	77.5	0.91 (0.68–1.21)
≥70 yr	86/500 (20.5)	83/469 (21.6)	−2.9	41.5	0.93 (0.63–1.39)
Respiratory support at entry					
No mechanical ventilation	203/2489 (9.4)	232/2475 (10.6)	−15.8	108.0	0.86 (0.67–1.11)
Mechanical ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**−8.3**	**148.8**	**0.95 (0.81–1.11)**
Heterogeneity around total: $\chi^2_3=3.9$					P=0.50



Nguồn: N Engl J Med 2021;384:497-511



OR = 0,95 (KTC 95%, 0,81-1,11), p=0,50

Ảnh hưởng của Remdesivir lên tử vong

Remdesivir (GS-5734)

Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20

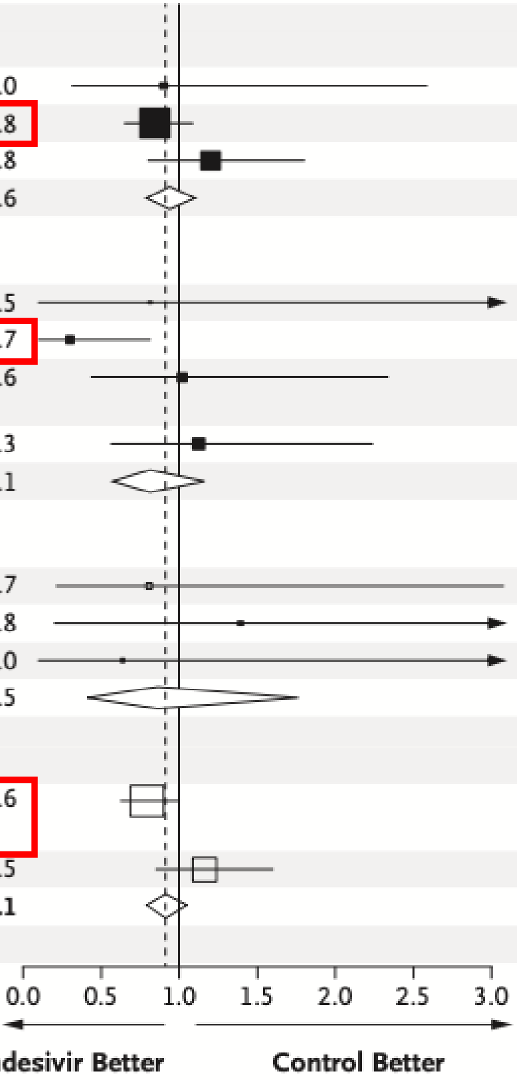


Figure 4. Meta-Analysis of Mortality in Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19.

Các thuốc kháng virus ít/không có hiệu quả đối với bệnh nhân SARS-CoV-2 (tử vong, nhu cầu thở máy, thời gian nằm viện)

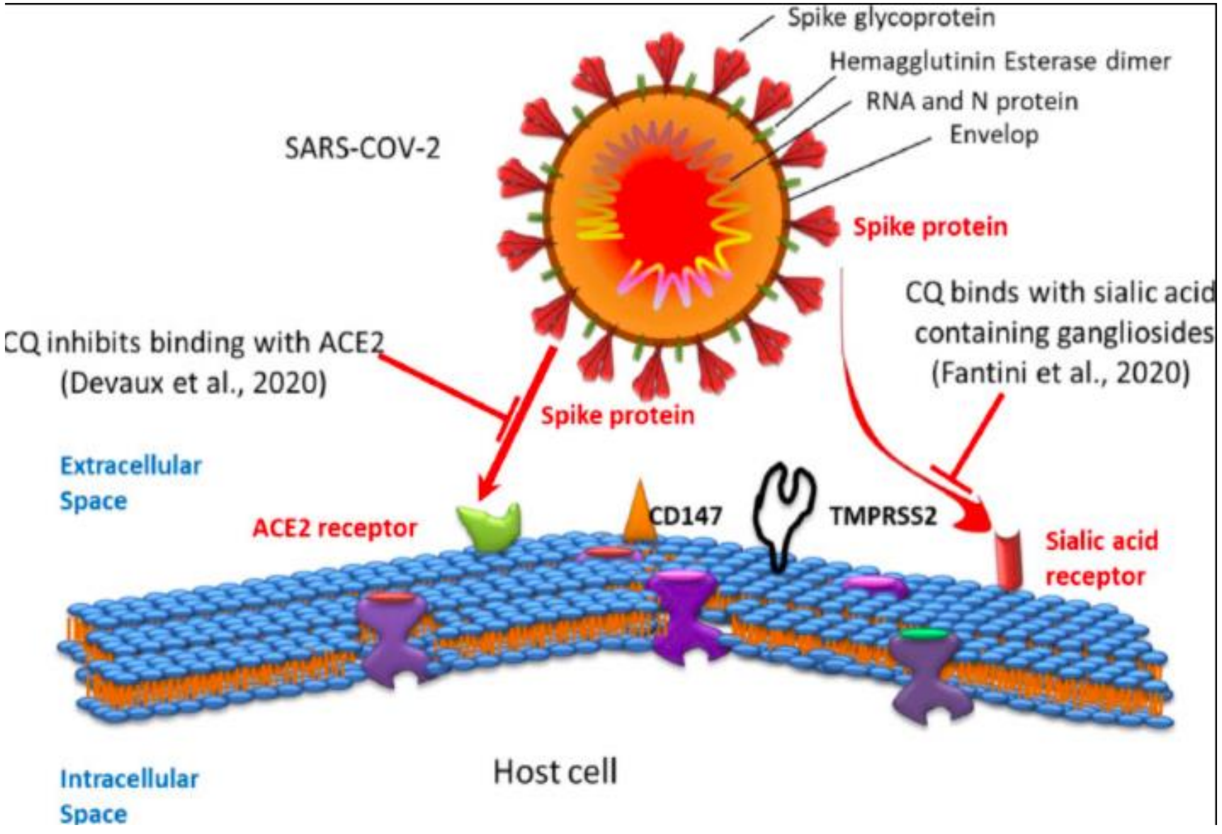
Nguồn: N Engl J Med 2021;384:497-511

CHLOROQUINE VÀ HYDROXYCHLOROQUINE

- Chloroquine là thuốc điều trị sốt rét từ năm 1934.
- Hydroxychloroquine là thuốc điều trị sốt rét và các bệnh tự miễn (lupus ban đỏ, viêm khớp dạng thấp).
- Nhiều cơ chế tác động ngăn cản virus xâm nhập vào tế bào.
- NC *in vitro* của Yao: SARS-CoV-2 bị ức chế bởi CQ ở $EC_{50} = 5,47$ uM >> HCQ ở $EC_{50} = 0,42$ uM.
- Khi dịch mới bùng phát, HCQ là một thuốc đầy hứa hẹn vì hoạt tính điều hòa miễn dịch và kháng virus *in vitro*. [(1)]

(1): Appl Microbiol Biotech 2021

CƠ CHẾ TÁC ĐỘNG



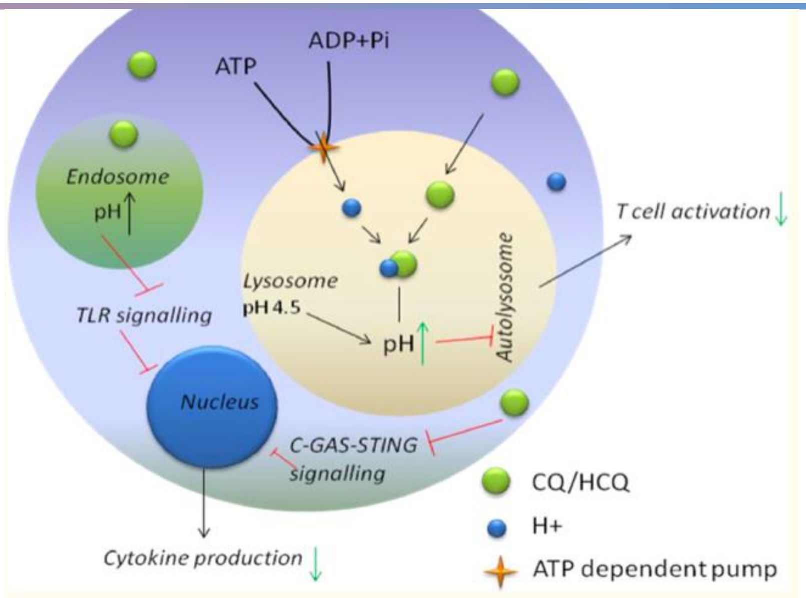


Fig. 2

Schematic diagram of the role of chloroquine (CQ) and hydroxychloroquine (HCQ) in the intracellular space. The drugs increase the pH of endosomes and lysosomes. As a result, activation of T-cells and other cytokines is repressed.

(1) Tăng pH nội sinh các endosome, làm giảm khả năng xâm nhập, nhân lên và lây nhiễm của virus
(2) Can thiệp vào quá trình glycosyl hóa các receptor
(3) Giảm quá trình tự thực bào
(4) Điều hòa miễn dịch

Nguồn: A review on possible modes of actions of Chloroquine/Hydroxychloroquine: Repurposing against SAR-COV-2 (COVID 19) pandemic. International Journal of Antimicrobial Agents (2020)

CHLOROQUINE VÀ HYDROXYCHLOROQUINE

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret [a, b, $], Jean-Christophe Lagier [a, c, $], Philippe Parola [a, b], Van Thuan Hoang [a, b, d], Line Meddeb [a], Morgane Mailhe [a], Barbara Doudier [a], Johan Courjon [e, f, g], Valérie Giordanengo [h], Vera Esteves Vieira [a], Hervé Tissot Dupont [a, c], Stéphane Honoré [i, j], Philippe Colson [a, c], Eric Chabrière [a, c], Bernard La Scola [a, c], Jean-Marc

- 20 BN dùng HCQ (600mg/ngày) và 16 BN không dùng.
- Tỷ lệ thanh thải virus vào Ngày 6 đạt 70% ở nhóm HCQ và 12,5% ở nhóm chứng.
- Hạn chế: đánh giá hiệu quả dựa vào vi sinh mà không dựa vào đáp ứng lâm sàng.

Results: Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the litterature for untreated patients. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

Conclusion: Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

Nguồn: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (2020)

March 28, 2020

APPROVED

Dr. Rick Bright, Ph.D.
Director
Biomedical Advanced Research a
Office of Assistant Secretary for I
U.S. Department of Health and H
330 Independence Ave, S.W.
Room 640G
Washington, D.C. 20201

Re: Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease

1. The SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that chloroquine phosphate and hydroxychloroquine sulfate may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of chloroquine phosphate and hydroxychloroquine sulfate when used to treat COVID-19 outweigh the known and potential risks of such products; and
3. There is no adequate, approved, and available alternative to the emergency use of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of COVID-19.[6]

CHLOROQUINE VÀ HYDROXYCHLOROQUINE

Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study

Sherief Abd-Elsalam [1], Eslam Saber Esmail [1], Mai Khalaf [1], Ehab Fawzy Abdo [2], Mohammed A Medhat [2], Mohamed Samir Abd El Ghafar [3], Ossama Ashraf Ahmed [4], Shaimaa Soliman [5], Ghada N Serangawy [6], Mohamed Alboraie [7]

- P: 194 bệnh nhân SARS-CoV-2 ở nhiều mức độ nhẹ, trung bình, nặng.
- I+C: Chia ngẫu nhiên thành 97 BN dùng HCQ và 97 BN điều trị chuẩn.
- O:

✓ **Hồi phục trong 28 ngày**: 53,6% vs. 34% (p = 0,06)

✓ **Nhu cầu thở máy**: 4,1% vs. 5,2% (p = 0,75)

✓ **Tử vong**: 6,2% vs. 5,2% (p = 0,76)

Clinical course in both groups

Clinical course	Hydroxychloroquine (n = 97)	Control (n = 97)	P-value
Disease severity after 28 days, n (%)			
Recovered	52 (53.6)	33 (34.0)	0.06
Mild	23 (23.7)	39 (40.2)	
Moderate	8 (8.2)	11 (11.3)	
Severe	8 (8.2)	9 (9.2)	
Death	6 (6.1)	5 (5.1)	
Need for ICU	11 (11.3)	13 (13.4)	0.83
Duration to negative PCR, mean ± SD	17.01 ± 2.98	17.64 ± 2.45	0.11
Duration to clinical improvement, mean ± SD	9.43 ± 1.87	9.52 ± 2.94	0.80
Duration to hospital discharge, mean ± SD	11.04 ± 2.71	11.27 ± 2.19	0.52

Nguồn: *Am J Trop Med Hyg*. 2020 Oct; 103(4): 1635–1639.

CHLOROQUINE VÀ HYDROXYCHLOROQUINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

A.B. Cavalcanti, F.G. Zampieri, R.G. Rosa, L.C.P. Azevedo, V.C. Veiga, A. Avezum, L.P. Damiani, A. Marcadenti, L. Kawano-Dourado, T. Lisboa, D.L.M. Junqueira, P.G.M. de Barros e Silva, L. Tramujas, E.O. Abreu-Silva, L.N. Laranjeira, A.T. Soares, L.S. Echenique, A.J. Pereira, F.G.R. Freitas, O.C.E. Gebara, V.C.S. Dantas, R.H.M. Furtado, E.P. Milan, N.A. Golin, F.F. Cardoso, I.S. Maia, C.R. Hoffmann Filho, A.P.M. Kormann, R.B. Amazonas, M.F. Bocchi de Oliveira, A. Serpa-Neto, M. Falavigna, R.D. Lopes, F.R. Machado, and O. Berwanger, for the Coalition Covid-19 Brazil I Investigators*

- **P:** 504 BN nhiễm SARS-CoV-2 nhẹ-TB (không thở oxy hoặc thở <= 4 l/ph).
- **I+C:** chia thành 3 nhóm (1:1:1) gồm dùng HCQ đơn thuần; nhóm HCQ + AZM và "standard care".
- **O:** Đánh giá tình trạng lâm sàng vào N15 thông qua "7-level Ordinal scale"

Nguồn: N Engl J Med 2020; 383:2041-2052

RESULTS

A total of 667 patients underwent randomization; 504 patients had confirmed Covid-19 and were included in the modified intention-to-treat analysis. As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P=1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P=1.00). Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent.

CONCLUSIONS

Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care. (Funded by the Coalition Covid-19 Brazil and EMS Pharma; ClinicalTrials.gov number, NCT04322123.)

CHLOROQUINE VÀ HYDROXYCHLOROQUINE - RECOVERY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

Table 2. Primary and Secondary Outcomes.

Outcome	Hydroxychloroquine (N=1561)	Usual Care (N=3155)	Rate or Risk Ratio (95% CI)
	no./total no. (%)		
Primary outcome: 28-day mortality	421/1561 (27.0)	790/3155 (25.0)	1.09 (0.97–1.23)*
Secondary outcomes			
Discharge from hospital in ≤28 days	931/1561 (59.6)	1983/3155 (62.9)	0.90 (0.83–0.98)*
Invasive mechanical ventilation or death†	399/1300 (30.7)	705/2623 (26.9)	1.14 (1.03–1.27)‡
Invasive mechanical ventilation	128/1300 (9.8)	225/2623 (8.6)	1.15 (0.93–1.41)
Death	311/1300 (23.9)	574/2623 (21.9)	1.09 (0.97–1.23)

Nguồn: N Engl J Med 2020;383:2030-40.

Subgroup	Hydroxychloroquine	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Age			
<70 yr	160/925 (17.3)	314/1873 (16.8)	1.03 (0.85–1.25)
≥70 to <80 yr	128/342 (37.4)	207/630 (32.9)	1.17 (0.93–1.47)
≥80 yr	133/294 (45.2)	269/652 (41.3)	1.14 (0.92–1.42)
Sex			
Male	276/960 (28.8)	543/1974 (27.5)	1.05 (0.91–1.22)
Female	145/601 (24.1)	247/1181 (20.9)	1.19 (0.96–1.47)
Race or ethnic group			
White	335/1181 (28.4)	610/2298 (26.5)	1.09 (0.95–1.25)
Black, Asian, or minority ethnic group	65/264 (24.6)	115/593 (19.4)	1.32 (0.96–1.81)
Days since symptom onset			
≤7	177/622 (28.5)	339/1275 (26.6)	1.10 (0.91–1.32)
>7	242/930 (26.0)	445/1871 (23.8)	1.11 (0.94–1.30)
Respiratory support at randomization			
No oxygen received	58/362 (16.0)	99/750 (13.2)	1.24 (0.89–1.73)
Oxygen only	253/938 (27.0)	475/1873 (25.4)	1.08 (0.93–1.26)
Invasive mechanical ventilation	110/261 (42.1)	216/532 (40.6)	1.03 (0.81–1.30)
Baseline risk			
<30%	146/994 (14.7)	274/1990 (13.8)	1.07 (0.88–1.32)
≥30% to <45%	135/317 (42.6)	246/635 (38.7)	1.12 (0.90–1.40)
≥45%	140/250 (56.0)	270/530 (50.9)	1.17 (0.95–1.45)
All Participants	**421/1561 (27.0)**	**790/3155 (25.0)**	**1.09 (0.97–1.23)** P=0.15

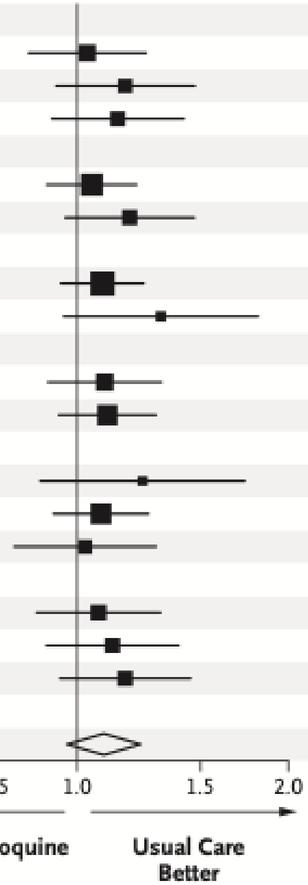


Figure 3. Mortality at 28 Days, According to Subgroup.

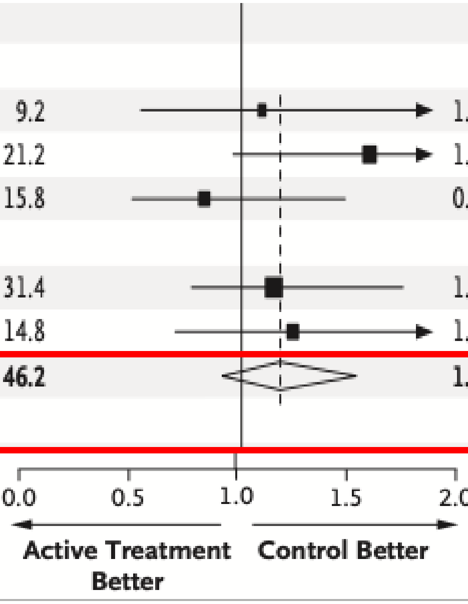
CHLOROQUINE VÀ HYDROXYCHLOROQUINE - SOLIDARITY

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

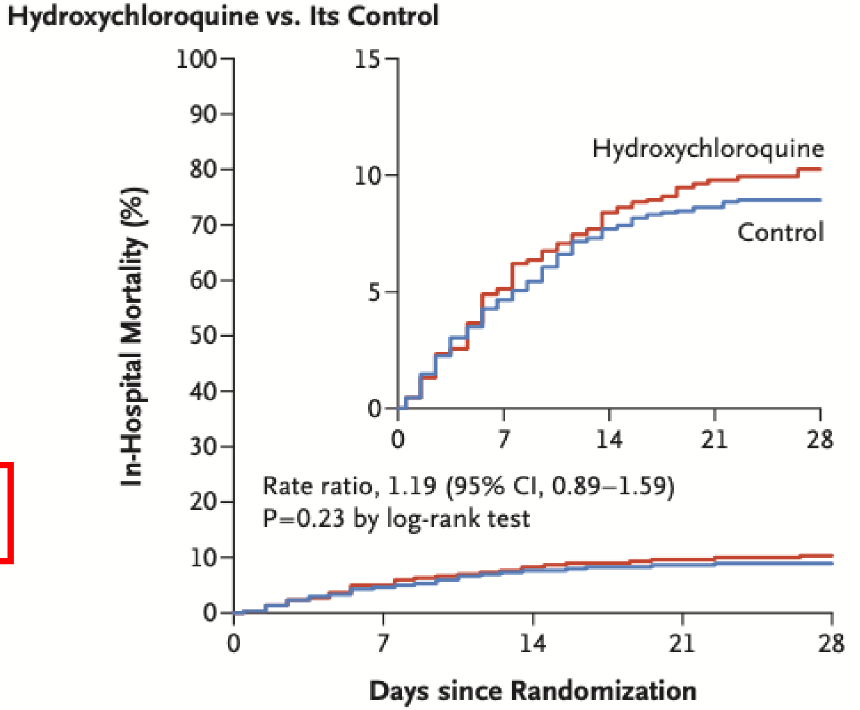
WHO Solidarity Trial Consortium*

Hydroxychloroquine					
Age at entry					
<50 yr	19/335 (5.7)	19/317 (5.8)	0.9	9.2	1.10 (0.47–2.57)
50–69 yr	55/410 (12.1)	31/396 (7.1)	10.8	21.2	1.66 (0.95–2.91)
≥70 yr	30/202 (14.0)	34/193 (17.8)	-3.5	15.8	0.80 (0.42–1.53)
Respiratory support at entry					
No mechanical ventilation	69/862 (7.4)	57/824 (6.6)	4.7	31.4	1.16 (0.73–1.84)
Mechanical ventilation	35/85 (39.2)	27/82 (32.3)	3.4	14.8	1.26 (0.65–2.46)
Total	**104/947 (10.2)**	**84/906 (8.9)**	**8.1**	**46.2**	**1.19 (0.89–1.59)**
Heterogeneity around total: $\chi^2_3=5.0$					P=0.23



Nguồn: N Engl J Med 2021;384:497-511

11330 BN từ 30 quốc gia:
- 2750 BN dùng RDV
- 954 BN dùng HCQ
- 1411 BN dùng LPV/r
- 2063 BN dùng interferon (gồm 651 LPV)



TÍNH HIỆU QUẢ VÀ AN TOÀN CỦA CQ/HCQ

- Các RCT lớn (RECOVERY, SOLIDARITY) cho thấy HCQ không làm giảm tử vong, nhu cầu thở máy và thời gian nằm viện.
- Vài NC chỉ đánh giá hiệu quả dựa vào thanh thải lượng virus mà không dựa vào đáp ứng lâm sàng.
- Trong các đợt dịch trước (Chikungunya, SXH, cúm), tác dụng kháng virus *in vitro* nhưng không có tác dụng trên lâm sàng.
- Tác dụng phụ: nghiêm trọng (QT kéo dài, tán huyết ở BN thiếu G6PD, tổn thương võng mạc), thường gặp (chuột rút, buồn nôn, tiêu chảy).

U.S. FOOD & DRUG ADMINISTRATION

VÌ SAO CQ/HCQ BỊ FDA LOẠI BỎ?

June 15, 2020

Page 2 – BARDA

- We now believe that the suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.
- Earlier observations of decreased viral shedding with HCQ or CQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone.
- Current U.S. treatment guidelines do not recommend the use of CQ or HCQ in hospitalized patients with COVID-19 outside of a clinical trial, and the NIH guidelines now recommend against such use outside of a clinical trial.

  Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.

FDA has concluded that, based on this new information and other information discussed in the attached memorandum, it is no longer reasonable to believe that oral formulations of HCQ and CQ may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks. Accordingly, FDA revokes the EUA for emergency use of HCQ and CQ to treat COVID-19, pursuant to section 564(g)(2) of the Act. As of the date of this letter, the oral formulations of HCQ and CQ are no longer authorized by FDA to treat COVID-19.

Nguồn: fda.gov

HCQ/CQ: CÁNH CỬA ĐÃ KHÉP LẠI?

Hydroxychloroquine COVID-19 RCTs excluding late treatment

hcqmeta.com 6/4/21

		Treatment	Control	RR	CI	
Huang (RCT)	no recov.	0/10	6/12	0.08	[0.01-1.32]	
Chen (RCT)	viral time	18/18	12/12	0.28	[0.10-0.82]	
Mitjà (RCT)	hosp.	8/136	11/157	0.84	[0.35-2.03]	
Skipper (RCT)	hosp./death	5/231	8/234	0.63	[0.21-1.91]	
Omrani (RCT)	hosp.	7/304	4/152	0.88	[0.26-2.94]	
Amaravadi (DB RCT)	no recov.	3/15	6/12	0.40	[0.13-1.28]	
Early treatment		41/714	47/579	0.54	[0.33-0.86]	46% improvemer

$Tau^2 = 0.01; I^2 = 2.1\%$

		Treatment	Control	RR	CI	
Grau-Pujol (RCT)	cases	0/142	1/127	0.32	[0.01-7.80]	
Rajasingham (RCT)	hosp.	1/989	1/494	0.50	[0.03-7.97]	
Abella (RCT)	cases	4/64	4/61	0.95	[0.25-3.63]	
Rojas-Se.. (DB RCT)	symp. case	1/62	6/65	0.18	[0.02-1.59]	
Syed (RCT)	symp. case	10/48	6/46	1.60	[0.63-4.04]	
PrEP		16/1,305	18/793	0.92	[0.44-1.91]	8% improvemer

$Tau^2 = 0.06; I^2 = 6.8\%$

		Treatment	Control	RR	CI	
Boulware (RCT)	cases	49/414	58/407	0.83	[0.58-1.18]	
Mitjà (RCT)	death	4/1,196	9/1,301	0.48	[0.15-1.57]	
Barnabas (RCT)	hosp.	1/407	1/422	1.04	[0.07-16.5]	
Seet (CLUS. RCT)	severe case	29/432	64/619	0.65	[0.43-0.99]	
PEP		83/2,449	132/2,749	0.74	[0.57-0.96]	26% improvement

$Tau^2 = 0.00; I^2 = 0.0\%$

All studies		140/4,468	197/4,121	0.71	[0.57-0.88]	29% improvement

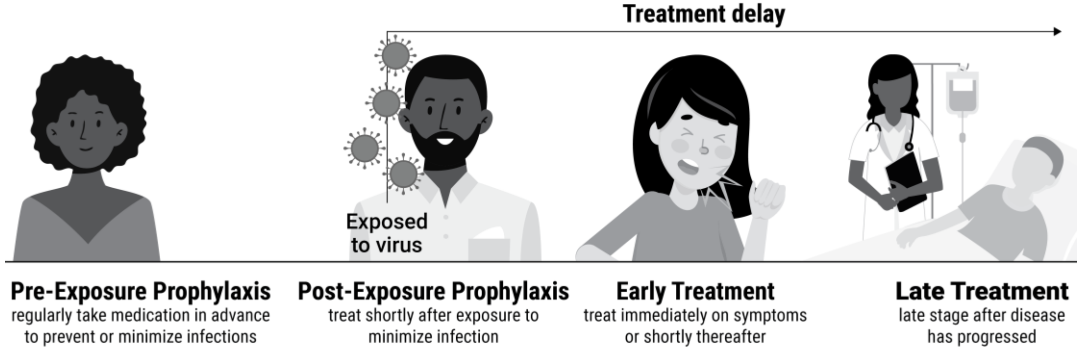
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+

$Tau^2 = 0.00; I^2 = 0.0\%; Z = 3.12\ (p = 0.0009)$

Lower Risk Increased Risk C

		Treatment	Control	RR	CI	
Chen (RCT)	progression	5/15	7/15	0.71	[0.29-1.74]	
Chen (RCT)	pneumonia	6/31	14/31	0.43	[0.19-0.97]	
Tang (RCT)	viral+	11/75	14/75	0.79	[0.38-1.62]	
RECOVERY (RCT)	death	421/1,561	790/3,155	1.09	[0.97-1.23]	
Chen (RCT)	viral+	4/21	3/12	0.76	[0.20-2.84]	
Lyngbakken (RCT)	death	1/27	1/26	0.96	[0.06-14.6]	
Cavalcanti (RCT)	death	8/331	5/173	0.84	[0.28-2.53]	
Abd-Elsalam (RCT)	death	6/97	5/97	1.20	[0.38-3.80]	
Ulrich (RCT)	death	7/67	6/61	1.06	[0.38-2.98]	
Ader (RCT)	death	11/145	12/148	0.94	[0.43-2.05]	
SOLIDARITY (RCT)	death	104/947	84/906	1.19	[0.89-1.59]	
Dubee (RCT)	death	6/124	11/123	0.54	[0.21-1.42]	
Self (RCT)	death	25/241	25/236	1.06	[0.57-1.87]	
Johnston (RCT)	hosp.	5/148	4/83	0.70	[0.19-2.54]	
Hernandez-C.. (RCT)	death	106	108	0.88	[0.51-1.53]	
Purwati (DB RCT)	viral+	38/121	111/119	0.34	[0.26-0.44]	
Gonzalez (DB RCT)	death	2/33	6/37	0.37	[0.08-1.73]	
Reis (DB RCT)	death	0/214	1/227	0.34	[0.01-8.30]	
Réa-Neto (RCT)	death	16/53	10/52	1.57	[0.79-3.13]	
Bosaeed (RCT)	death	14/125	15/129	0.96	[0.49-1.91]	
Late treatment		690/4,482	1,124/5,813	0.81	[0.62-1.07]	19% improvement

$Tau^2 = 0.19; I^2 = 75.5\%$



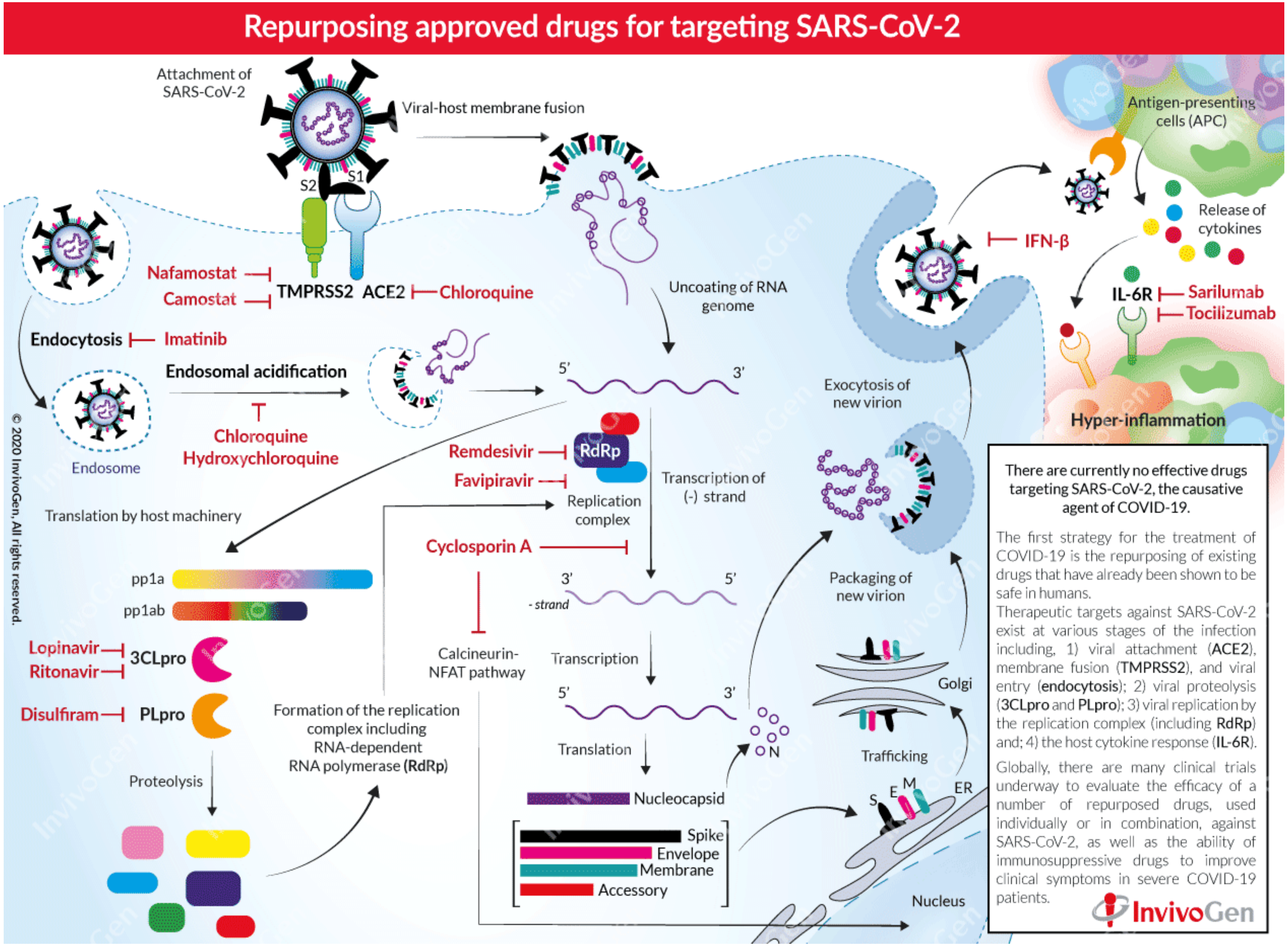
LOPINAVIR/RITONAVIR (LPV/r)

- LPV/r được dùng để điều trị HIV-1 nhờ hoạt tính ức chế enzym HIV aspartate protease.
- LPV bị chuyển hóa mạnh bởi hệ CYP3A4. Ritonavir là chất ức chế CYP3A4 nên giúp tăng $T_{1/2}$ của LPV.
- Có hoạt tính kháng virus SARS-CoV *in vitro*[1,2], giảm kết cục xấu (ARDS, tử vong) và giảm tải lượng virus ở bệnh nhân SARS [1].
- Có hoạt tính kháng MERS-CoV *in vitro*[3] và mô hình động vật[4]. Các báo cáo ca cho thấy LPV/r giúp giảm tử vong, tải lượng virus [5,6]

(1): *Thorax* (2004); 59:252-6. (2): *J Clin Virol* (2004); 31:69-75.
(3): *Antimicrob Agents Chemother* (2014); 58:4875-84
(4): J Infect Dis (2015); 212:1904-13.
(5): *Antivir Ther* 2016;21:455-9. (6): Sci Rep 2016;6: 25359.

LOPINAVIR/RITONAVIR

LPV/r ức chế hoạt tính enzym 3-chymotrypsin **(3CLpro)**, một enzym quan trọng giúp phân cắt các polypeptide (pp1a và pp1ab) thành các protein "effector"



Nguồn: www.invivogen.com/spotlight-covid-19- treatment-repurposed-drugs

LOPINAVIR/RITONAVIR – LOTUS China

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 7, 2020 VOL. 382 NO. 19

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

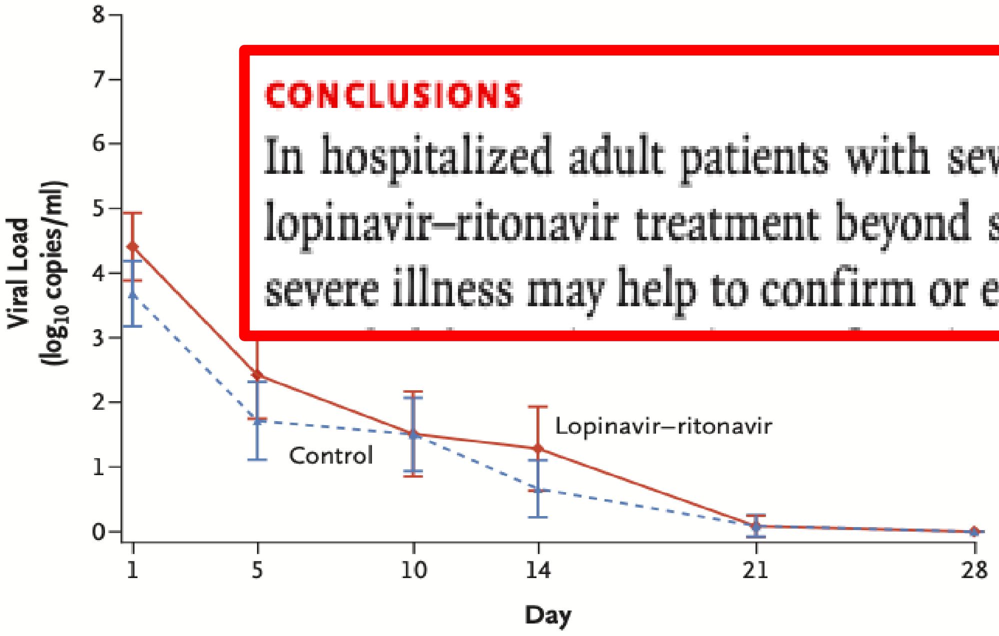


Figure 3. Mean Change from Baseline in SARS-CoV-2 Viral RNA Load by qPCR on Throat Swabs.

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.

Table 3. Outcomes in the Intention-to-Treat Population.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Time to clinical improvement — median no. of days (IQR)	16.0 (15.0 to 17.0)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)‡
Day 28 mortality — no. (%)	44 (22.1)	19 (19.2)§	25 (25.0)	−5.8 (−17.3 to 5.7)
Earlier (≤12 days after onset of symptoms)	21 (23.3)	8 (19.0)	13 (27.1)	−8.0 (−25.3 to 9.3)
		19.3)	12 (23.1)	−3.8 (−19.1 to 11.6)
		6.1)	2 (2.0)	4.1 (−1.4 to 9.5)
		45.5)	30 (30.0)	15.5 (2.2 to 28.8)
		78.8)	70 (70.0)	8.8 (−3.3 to 20.9)
(IQR)		to 11)	11 (7 to 17)	−5 (−9 to 0)
Of survivors	10 (8 to 17)	9 (5 to 44)	11 (9 to 14)	−1 (−16 to 38)
Of nonsurvivors	10 (4 to 14)	6 (2 to 11)	12 (7 to 17)	−6 (−11 to 0)
Duration of invasive mechanical ventilation — median no. of days (IQR)	5 (3 to 9)	4 (3 to 7)	5 (3 to 9)	−1 (−4 to 2)
Oxygen support — days (IQR)	13 (8 to 16)	12 (9 to 16)	13 (6 to 16)	0 (−2 to 2)
Hospital stay — median no. of days (IQR)	15 (12 to 17)	14 (12 to 17)	16 (13 to 18)	1 (0 to 2)

Nguồn: N Engl J Med 2020;382:1787-99.

LOPINAVIR/RITONAVIR

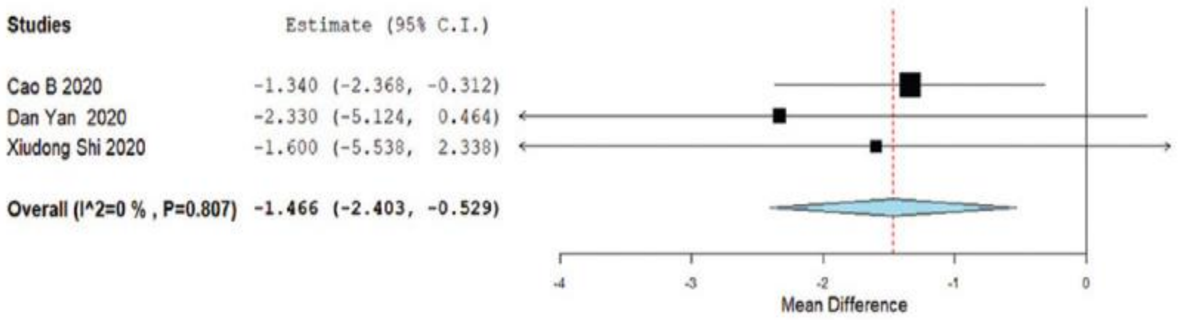
Safety and efficacy of lopinavir/ritonavir combination in COVID-19: A systematic review, meta-analysis, and meta-regression analysis

Anusuya Bhattacharyya [1], Subodh Kumar [2], Phulen Sarma [2], Hardeep Kaur [2], Manisha Prajapat [2], Nishant Shekhar [2], Seema Bansal [2], Pramod Avti [3], Mythili Hazarika [4], Saurabh Sharma [2], Dhruv Mahendru [2], Ajay Prakash [2], Bikash Medhi [2]

- Khảo sát từ 13 NC (5 RCTs + 8 NC quan sát/so sánh)
- So sánh LPV/r vs. Standard care/Thuốc kháng virus khác:

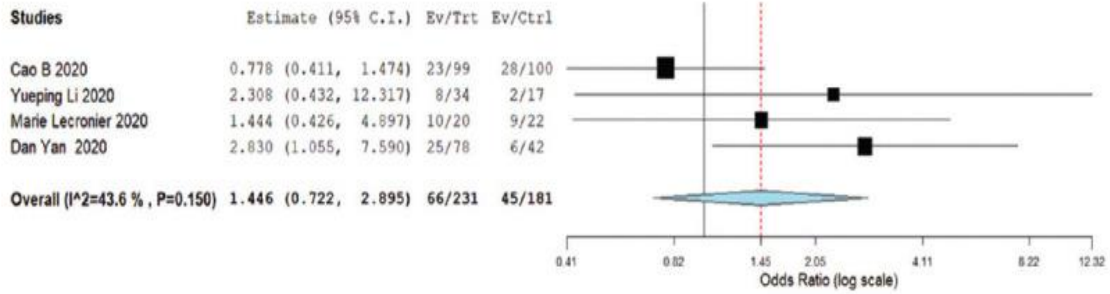
1. Thanh thải virus
2. Tử vong
3. Đáp ứng lâm sàng

Figure 2



Lopinavir + ritonavir versus standard of care: Duration of hospital stay

Figure 4



Lopinavir + ritonavir versus standard of care: Progression to severe disease

Nguồn: *Indian J Pharmacol* (2020) ; 52(4): 313–323.

LOPINAVIR/RITONAVIR - SOLIDARITY

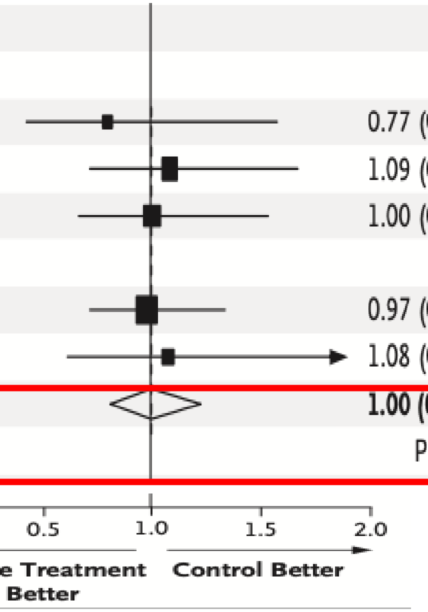
11330 BN từ 30 quốc gia:
- 2750 BN dùng RDV
- 954 BN dùng HCQ
- 1411 BN dùng LPV/r
- 2063 BN dùng interferon (gồm 651 LPV)

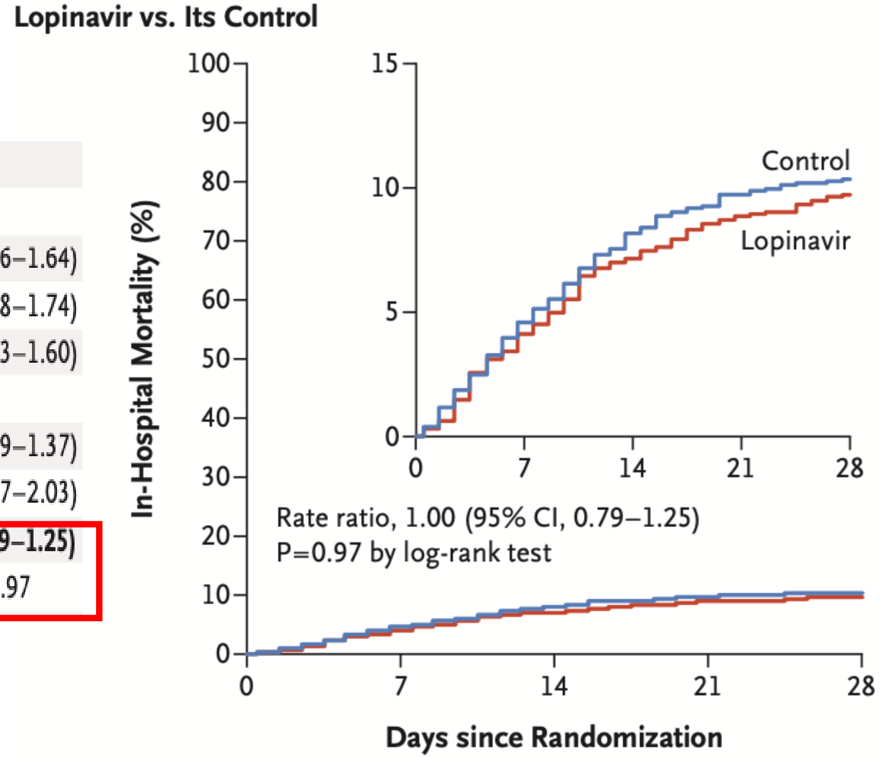
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

Lopinavir					
Age at entry					
<50 yr	20/511 (3.6)	27/501 (4.9)	−3.0	11.7	0.77 (0.36–1.64)
50–69 yr	66/597 (9.8)	57/596 (9.1)	2.7	30.4	1.09 (0.68–1.74)
≥70 yr	62/291 (20.4)	62/275 (22.7)	0.0	30.2	1.00 (0.63–1.60)
Respiratory support at entry					
No mechanical ventilation	113/1287 (8.1)	111/1258 (8.7)	−1.6	55.6	0.97 (0.69–1.37)
Mechanical ventilation	35/112 (28.1)	35/114 (28.7)	1.3	16.7	1.08 (0.57–2.03)
Total	**148/1399 (9.7)**	**146/1372 (10.3)**	**−0.4**	**72.3**	**1.00 (0.79–1.25)**
Heterogeneity around total: $\chi^2_3=1.2$					P=0.97





Nguồn: N Engl J Med 2021;384:497-511

UMIFENOVIR (Arbidol)

- Arbidol được dùng để dự phòng và điều trị nhiễm cúm A, cúm B.(1)
- ARB gắn với glycoprotein hemagglutinin → ngăn chặn virus influenza xâm nhập vào TB. (2)
- Ngăn cản tương tác protein S – ACE2 → ngăn cản SARS-CoV-2 hòa màng.
- Có hiệu quả kháng Coronaviridae *in vitro*. (3)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results

Modify Search Start Over

14 Studies found for: **Arbidol | Covid19**

Nguồn: Sanders (2020). *JAMA*, 323(18), 1824-1836.

(1): Clin Microbiol Infect. 2020 Jul;26 (7):917–921
(2): Curr Med Chem. 2008;15(10):997–1005
(3): J Med Virol. 2012 Jan;84(1):170–181

UMIFENOVIR (Arbidol)

- **P:** 33 BN SARS-CoV-2 không thở máy
- **I+C:** LPV/r + ARB (C) vs. LPV/r (M)
- **O:**

✓ Sau 7 ngày, RT-PCR (-) 75% ở nhóm C, 35% ở nhóm M (p <0,05).

✓ Sau 14 ngày, RT-PCR (-) ở 94% nhóm C, 53% ở nhóm M (p <0,05).

✓ Cải thiện hình ảnh CT scan phổi sau 7 ngày là 69% (nhóm C) và 29% (nhóm M) với p <0,05 .

Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study

Lisi Deng[a,1], Chunna Li[a,1], Qi Zeng[b], Xi Liu[a], Xinghua Li[a], Haitang Zhang[a], Zhongsi Hong[a,*], Jinyu Xia[a,*]

[a] Department of Infectious Diseases, the Fifth Affiliated Hospital, Sun Yat-sen University, 52 East Meihua Road, Zhuhai 519000, Guangdong Province, China
[b] Cancer Center, the Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong Province, China

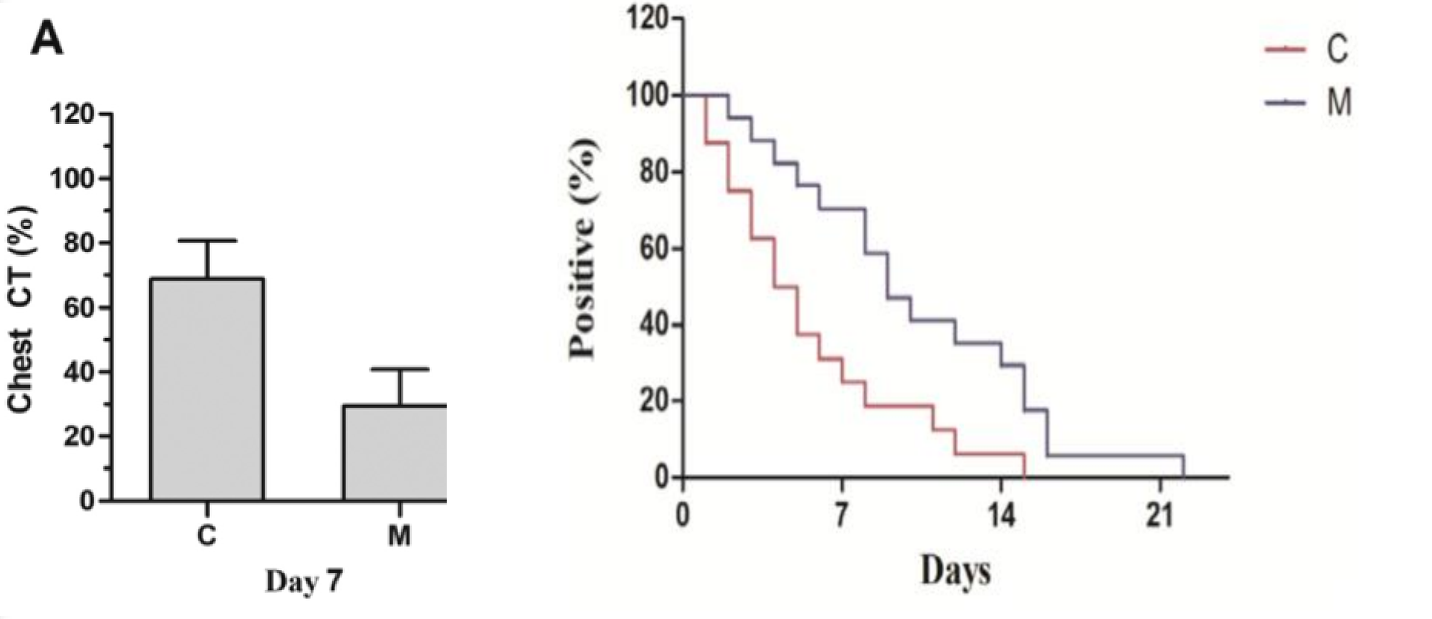


Fig. 2. Nasopharyngeal swab tests of SARS-CoV-2 nucleic acid by RT-PCR between two grous. Note: C refer to combination group; M refers to monotherapy group.

Nguồn: Journal of Infection 81 (2020) e1–e5

Original article

Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study

N. Lian [1, †], H. Xie [1, †], S. Lin [2], J. Huang [1], J. Zhao [1], Q. Lin [1, *]

[1)] *Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China*
[2)] *Liver Research Centre, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China*

- **P:** 81 BN nhiễm SARS-CoV-2 không nằm ICU
- **I+C:** 45 BN dùng Arbidol vs. 36 BN nhóm chứng
- **O:**

✓ Tỷ lệ RT-PCR (-) sau 7 ngày: 73% (ARB) vs 78% (control), p= 0,19.
✓ Thời gian chuyển âm: 18 ngày (ARB) vs. 16 ngày (control), p= 0,42
✓ Nằm viện: 13 ngày (ARB) vs. 11 ngày (control), p= 0,04.
✓ Tử vong: không khác biệt.

Table 2
Effectiveness of umifenovir in patients with COVID-19.

	Umifenovir group (n = 45)	Control group (n = 36)	p
CT score (after treatment)	7 (5–9)	5 (2–6)	0.01
CT score dif	3 (1–7)	3 (1–4)	0.52
Time from admission to first negative test of SARS-CoV-2 (days)	6 (4–8)	3 (1–7)	0.01
Time from onset of symptoms to first negative test of SARS-CoV-2 (days)	18 (12–21)	16 (11–21)	0.42
Negative rate of pharyngeal swab test for SARS-CoV-2 within 1 week	33 (73)	28 (78)	0.19
Length of hospital stay (days)	13 (9–17)	11 (9–14)	0.04

Table 3
Effectiveness of umifenovir in patients with moderate and severe COVID-19.

	Moderate			Severe		
	Umifenovir (n = 33)	Control (n = 18)	p	Umifenovir (n = 12)	Control (n = 18)	p
CT score (post treatment)	9 (6–10)	6 (3–7)	0.05	6 (5–8)	3 (1–5)	0.01
CT score dif	3 (1–7)	3 (1–4)	0.77	3 (1–8)	3 (2–6)	0.28
Time from admission to first negative test of SARS-CoV-2 (days)	5 (3–7)	1 (4–7)	0.24	7 (5–9)	2 (1–7)	0.02
Time from onset of symptoms to first negative test of SARS-CoV-2 (days)	17 (13–20)	17 (11–23)	0.93	19 (16–22)	17 (13–21)	0.19
Negative rate of pharyngeal swab's test for SARS-CoV-2 within 1 week	26 (79)	15 (83)	0.50	7 (64)	13 (72)	0.34
Length of hospital stay (days)	14 (9–17)	11 (8–14)	0.04	12 (10–15)	10 (9–15)	0.34

Nguồn: Clinical Microbiology and Infection 26 (2020).pp 917-921

Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial

Yueping Li,[1,6] Zhiwei Xie,[1,6] Weiyin Lin,[1,6] Weiping Cai,[1,6] Chunyan Wen,[1] Yujuan Guan,[1] Xiaoneng Mo,[3] Jian Wang,[1] Yaping Wang,[1] Ping Peng,[3] Xudan Chen,[1] Wenxin Hong,[1] Guangming Xiao,[1] Jinxin Liu,[5] Lieguang Zhang,[5] Fengyu Hu,[4] Feng Li,[4] Fuchun Zhang,[1,*] Xilong Deng,[2,**] and Linghua Li[1,7,***]

- **P:** 86 BN Covid-19 nhẹ-trung bình
- **I+C:** chia 3 nhóm LPV/r (34), ARB (35) và không thuốc (17)
- **O:** Tỷ lệ RT-PCR chuyển âm

Outcomes of the Three Groups (Intention-to-Treat Population)

Outcome	LPV/r	Arbidol	Control	p Value
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic	12/34	13/35	7/17	0.966
acid in pharyngeal swab, in days (mean/SD, 95% CI)	(7.2, 10.8)	(7.6, 10.6)	(6.7, 11.9)	
Conversion rate from moderate to severe/critical clinical status (%)	8/34 (23.5%)	3/35 (8.6%)	2/17 (11.8%)	0.206

Conclusions

LPV/r or arbidol monotherapy present little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care.

UMIFENOVIR (Arbidol)

- **P:** 100 BN viêm phổi do SARS-CoV-2 với $SpO_2 \leq 94\%$
- **I+C:** Chia ngẫu nhiên thành 2 nhóm (HCQ + LPV/r) và (HCQ + ARB)
- **O:**

✓ Thời gian nằm viện: 7,2 ngày (ARB) vs. 9,6 ngày (LPV/r), p=0,02.

✓ SpO_2 sau 7 ngày: 94% (ARB) vs. 92% (LPV/r), p= 0,02.

RESEARCH ARTICLE **Open Access**

Effect of Arbidol (Umifenovir) on COVID-19: a randomized controlled trial

Marzieh Nojomi[1], Zeynab Yassin[2], Hossein Keyvani[3], Mahin Jamshidi Makiani[4], Maryam Roham[4], Azadeh Laali[5], Nasir Dehghan[6], Mehrnaz Navaei[7] and Mitra Ranjbar[7*]

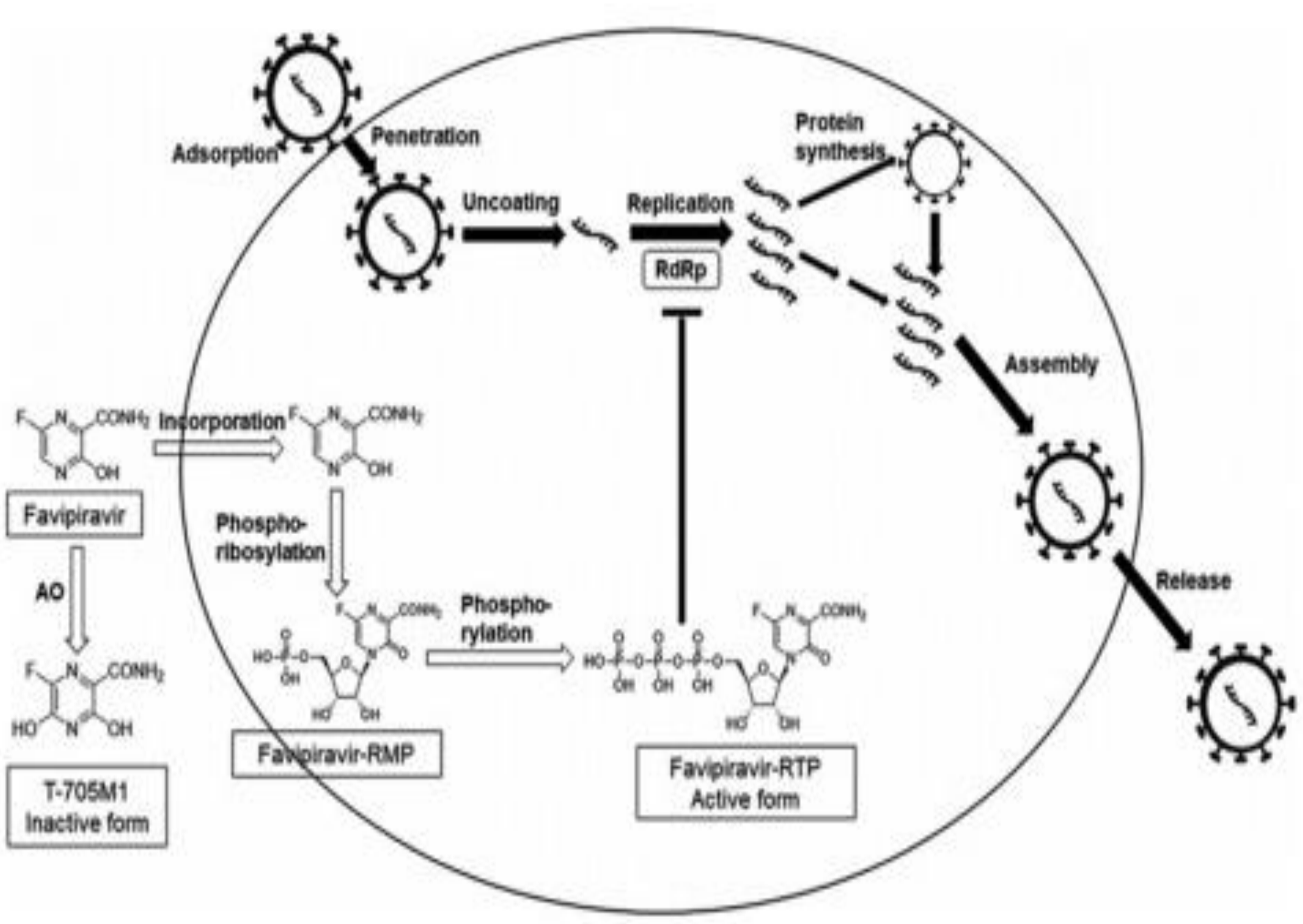
Results: The mean age of patients was 56.6 (17.8) years and 56.2 (14.8) years in ARB and KALETRA groups, respectively. Majority of patients were male across two groups (66 and 54%). The duration of hospitalization in ARB group was significantly less than KALETRA arm (7.2 versus 9.6 days; $P = 0.02$). Time to relief fever was almost similar across two groups (2.7 versus 3.1 days in ARB and KALETRA arms, respectively). Peripheral oxygen saturation rate was significantly different after 7 days of admission across two groups (94% versus 92% in ARB and KALETRA groups respectively) ($P = 0.02$). Based on multiple linear regression analysis, IHD, Na level, and oxygen saturation at the time of admission and type of therapy were the independent adjusted variables that determined the duration of hospitalization in patients with COVID-19.

Conclusion: Our findings showed that Arbidol, compared to KALETRA, significantly contributes to clinical and laboratory improvements, including peripheral oxygen saturation, requiring ICU admissions, duration of hospitalization, chest CT involvements, WBC, and ESR. We suggest further studies on ARB against COVID-19 using larger sample size and multicenter design.

Nguồn: BMC Infectious Diseases (2020) 20:954

FARIPIRAVIR (FPV)

- FPV dạng hoạt động có khả năng ức mạnh RdRp



Nguồn: International Journal of Infectious Diseases 102 (2021) 501–508

FARIPIRAVIR

Table 2
Summary of clinical evidence in patients with COVID-19 infection.

Author [reference]	Study type	Comparative studies				
		Variables	Favipiravir	vs.	Lopinavir/ritonavir[a]	p Value
Cai et al. (2020)	Interventional, open label, non-randomized clinical study	Viral clearance rate	4 days		11 days	<0.001
		Chest computed tomography	91.4%		62.2 %	0.004
		Adverse events	11.4%		55.6%	<0.001
		Variables	Favipiravir	vs.	Umifenovir	p Value
Chen et al. (2020)	Interventional, open label, randomized, and multicenter clinical trial	Clinical recovery rate at day 7	71.4%		55.8%	0.0199
		Latency for fever and cough relief	Significantly shorter		Higher	<0.0001
		Dyspnea after medication	3.5%		11.7%	0.0174

Single arm studies					
Study		Variables	Outcome at day 7	Variables	Outcome at day 14
Doi et al. (2020b)	Observational registry	Clinical recovery rate – mild	73.8%	Clinical recovery rate – mild	87.8%
		Clinical recovery rate – mod	66.6%	Clinical recovery rate – mod	84.5%
		<60 yrs.: clinical recovery rate	79.0%	<60 yrs.: clinical recovery rate	92.4%
Rattanaumpawan et al. (2020)	Multicenter observational study	Clinical improvement (without O2 supp.)	92.5%	-	-
		Clinical improvement (overall)	66.7%	-	-
		Poor prognostic factors by multivariate analysis	Lower favipiravir loading dose (≤45 mg/kg/day) (p = 0.006)	-	-

Nguồn: Role of favipiravir in the treatment of COVID-19 (2021)

FARIPIRAVIR

- **P:** 150 BN SARS-CoV-2 nhẹ-trung bình (Ấn Độ)
- **I+C:** Chia ngẫu nhiên (1:1) FPV vs. Control
- **O:**

✓ **Thời gian virus (-):** 5 ngày (FPV) vs. 7 ngày (control), p= 0,129

✓ **Thời gian hồi phục:** 3 ngày (FPV) vs. 5 ngày (control), p= 0,03.

✓ **Biến cố bất lợi:** 36% (FPV) vs. 8% (control)

Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial

Zarir F Udwadia [1], Pawan Singh [2], Hanmant Barkate [2], Saiprasad Patil [2], Shabbir Rangwala [2], Amol Pendse [2], Jatin Kadam [2], Wen Wu [3], Cynthia F Caracta [4], Monika Tandon [5]

Abstract

Objective: To assess the efficacy and safety of favipiravir in adults with mild-to-moderate coronavirus disease 2019 (COVID-19).

Methods: In this randomized, open-label, parallel-arm, multicenter, phase 3 trial, adults (18-75 years) with RT-PCR confirmed COVID-19 and mild-to-moderate symptoms (including asymptomatic) were randomized 1:1 to oral favipiravir (day 1: 1800 mg BID and days 2-14: 800 mg BID) plus standard supportive care versus supportive care alone. The primary endpoint was time to the cessation of viral shedding; time to clinical cure was also measured.

Results: From May 14 to July 3, 2020, 150 patients were randomized to favipiravir (n = 75) or control (n = 75). Median time to the cessation of viral shedding was 5 days (95% CI: 4 days, 7 days) versus 7 days (95% CI: 5 days, 8 days), P = 0.129, and median time to clinical cure was 3 days (95% CI: 3 days, 4 days) versus 5 days (95% CI: 4 days, 6 days), P = 0.030, for favipiravir and control, respectively. Adverse events were observed in 36% of favipiravir and 8% of control patients. One control patient died due to worsening disease.

Conclusion: The lack of statistical significance on the primary endpoint was confounded by limitations of the RT-PCR assay. Significant improvement in time to clinical cure suggests favipiravir may be beneficial in mild-to-moderate COVID-19.

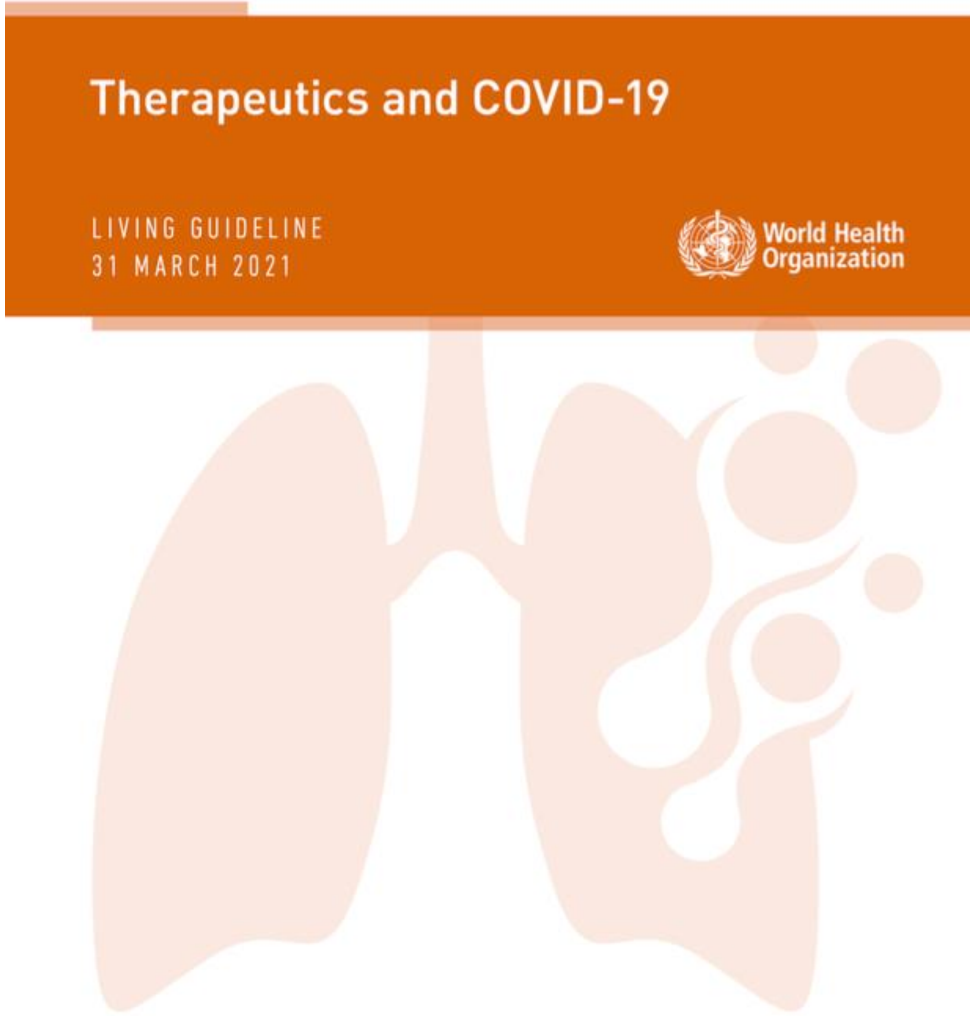
Nguồn: Int J Infect Dis (2021);103: 62-71.

FARIPIRAVIR

- Số lượng nghiên cứu TNLS còn hạn chế .
- NIH, WHO không đề cập vai trò của FPV.
- Được chấp thuận điều trị SARS-CoV-2 ở Trung Quốc từ 02/2020.
- FPV được khuyến cáo dùng để điều trị BN SARS-CoV-2 mức độ nhẹ - trung bình ở Nhật Bản, Saudi Arabia, Thái Lan…
- Các hướng dẫn của Nga cho phép dùng FPV để trị BN trung bình – nặng kết hợp với thuốc điều hòa miễn dịch.

Nguồn: Role of favipiravir in the treatment of COVID-19 (2021)

HƯỚNG DẪN CỦA WHO VỀ THUỐC KHÁNG VIRUS



Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Hospitalized patients with COVID-19 infection, regardless of disease severity

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection)

Conditional recommendation against

We suggest not to use corticosteroids.

For patients with severe or critical COVID-19-infection (see disease severity criteria above)

Recommended

We recommend systemic corticosteroids rather than no corticosteroids

HƯỚNG DẪN CỦA VIỆN Y TẾ QUỐC GIA HOA KỲ (NIH)

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)**. For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**
Hospitalized but Does Not Require Supplemental Oxygen	There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[a,b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[c] **plus remdesivir**[a,b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[d,e] • **Dexamethasone**[c] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[c] **(AI)**[e] • **Dexamethasone**[c] **plus remdesivir**[a,b] **(BIII)**[d,e] For patients who were recently hospitalized[f] with rapidly increasing oxygen needs and systemic inflammation: • Add **tocilizumab**[g] to one of the two options above **(BIIa)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	• **Dexamethasone**[c] **(AI)**[h] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[c] **plus tocilizumab**[g] **(BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

HƯỚNG DẪN CỦA SSC 2021 ĐIỀU TRỊ SARS-COV-2

TABLE 2.
Recommendations and Statements

Previous SSC COVID-19 Guideline — Recommendation/Statement	New SSC COVID-19 Guideline — Recommendation/Statement	Justification
Therapy		
No recommendation	2. For adults with severe or critical COVID-19, we recommend against using hydroxychloroquine (strong recommendation).	• Moderate-quality evidence showed no effect on mortality or need for mechanical ventilation
No recommendation	6. For adults with severe COVID-19 who do not require mechanical ventilation, we suggest using IV remdesivir over not using it (weak recommendation). *Remark*: Remdesivir should *ideally* be started within 72 hours of positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction or antigen testing.	• The result of a placebo-controlled trial showed large reduction in time to recovery and hospital stay • Subgroup analysis from the three trials showed a discordant effect on mortality, suggesting a possible reduction in death in patients who are not invasively ventilated • Despite cost and limited availability, we believe that many patients, if presented with data, would prefer to receive remdesivir
No recommendation	7. For adults undergoing mechanical ventilation for critical COVID-19, we suggest against starting IV remdesivir (weak recommendation).	• Limited data on the effect of remdesivir on outcomes of mechanically ventilated patients • Until more data is available, current costs and limited drug availability favor a weak recommendation against its use in this population

HƯỚNG DẪN SỐ 2008 CỦA BỘ Y TẾ 26/4/2021

BỘ Y TẾ

CỘNG HOÀ XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập - Tự do - Hạnh phúc

Số: 2008 /QĐ-BYT

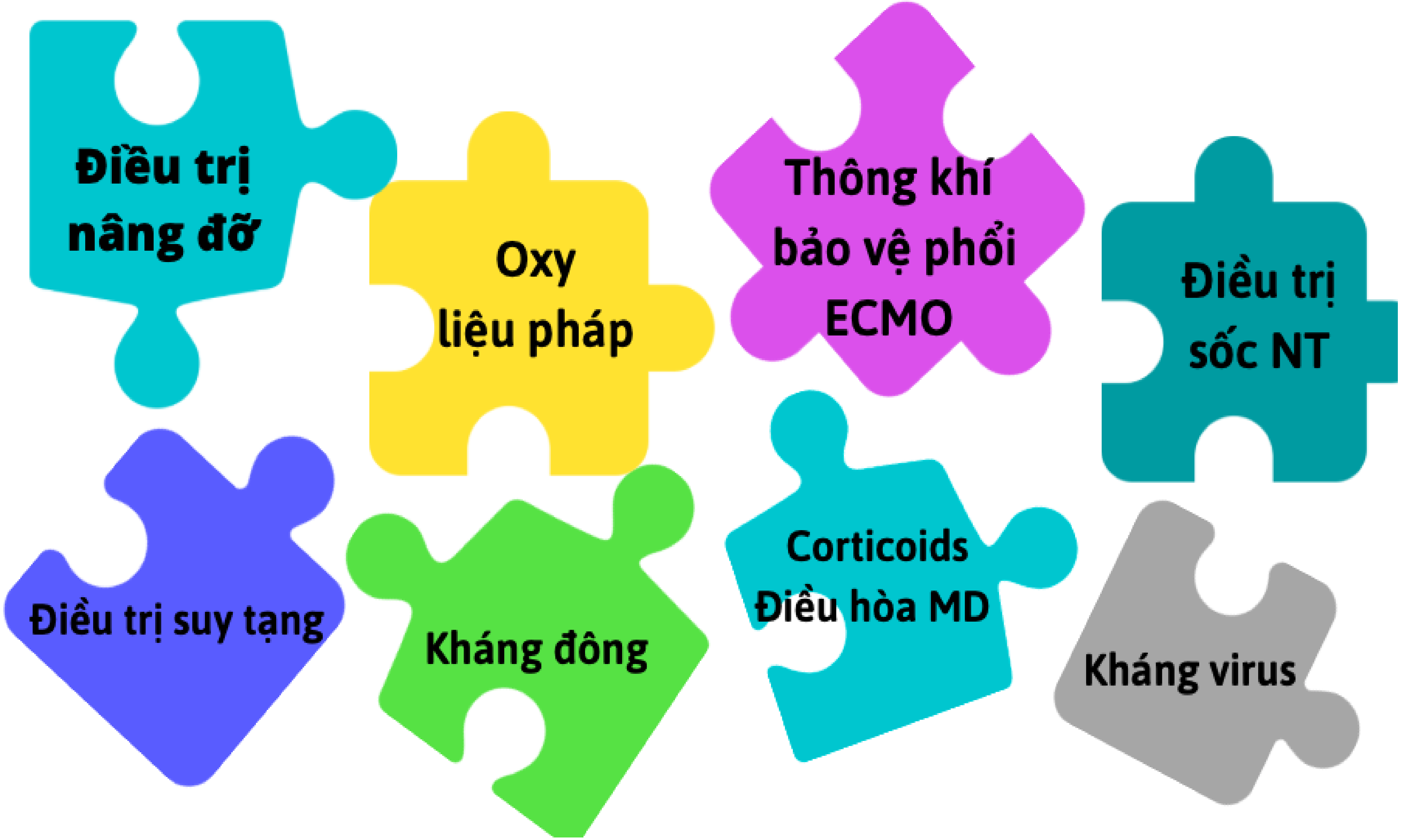
Hà Nội, ngày 26 tháng 04 năm 2021

QUYẾT ĐỊNH
Về việc ban hành Hướng dẫn chẩn đoán và điều trị COVID-19 do chủng vi rút Corona mới (SARS-CoV-2)

6.6. Thuốc kháng vi rút: Đã có nhiều thuốc được thử nghiệm nhưng chưa có hiệu quả rõ ràng.

TAKE HOME MESSAGES

- Cơ chế bệnh sinh của nhiễm SARS-CoV-2 gồm tấn công trực tiếp của virus và tác động bất lợi của quá trình đáp ứng MD quá mức.
- Những thuốc cũ trong thế giới mới.
- Thuốc kháng virus có 2 cơ chế tác động chính: ức chế virus xâm nhập và ức chế quá trình sao chép, tổng hợp virus mới.
- NIH khuyến cáo sử dụng RDV cho BN Covid-19 nhập viện cần hỗ trợ oxy lưu lượng thấp >> Thở HFNC/NIV.
- SSC đề xuất dùng RDV cho BN Covid-19 nặng, không thở máy.
- WHO và Bộ Y tế không khuyến cáo dùng thuốc kháng virus.


Điều trị nâng đỡ
Oxy liệu pháp
Thông khí bảo vệ phổi ECMO
Điều trị sốc NT
Điều trị suy tạng
Kháng đông
Corticoids Điều hòa MD
Kháng virus