Pharmacist as the Living Martindale; Power of Knowledge on antiviral information to prevent further spread and prompt treatment of COVID-19 Patients

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الجامعة الإسلامية العالمية ماليزيا

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

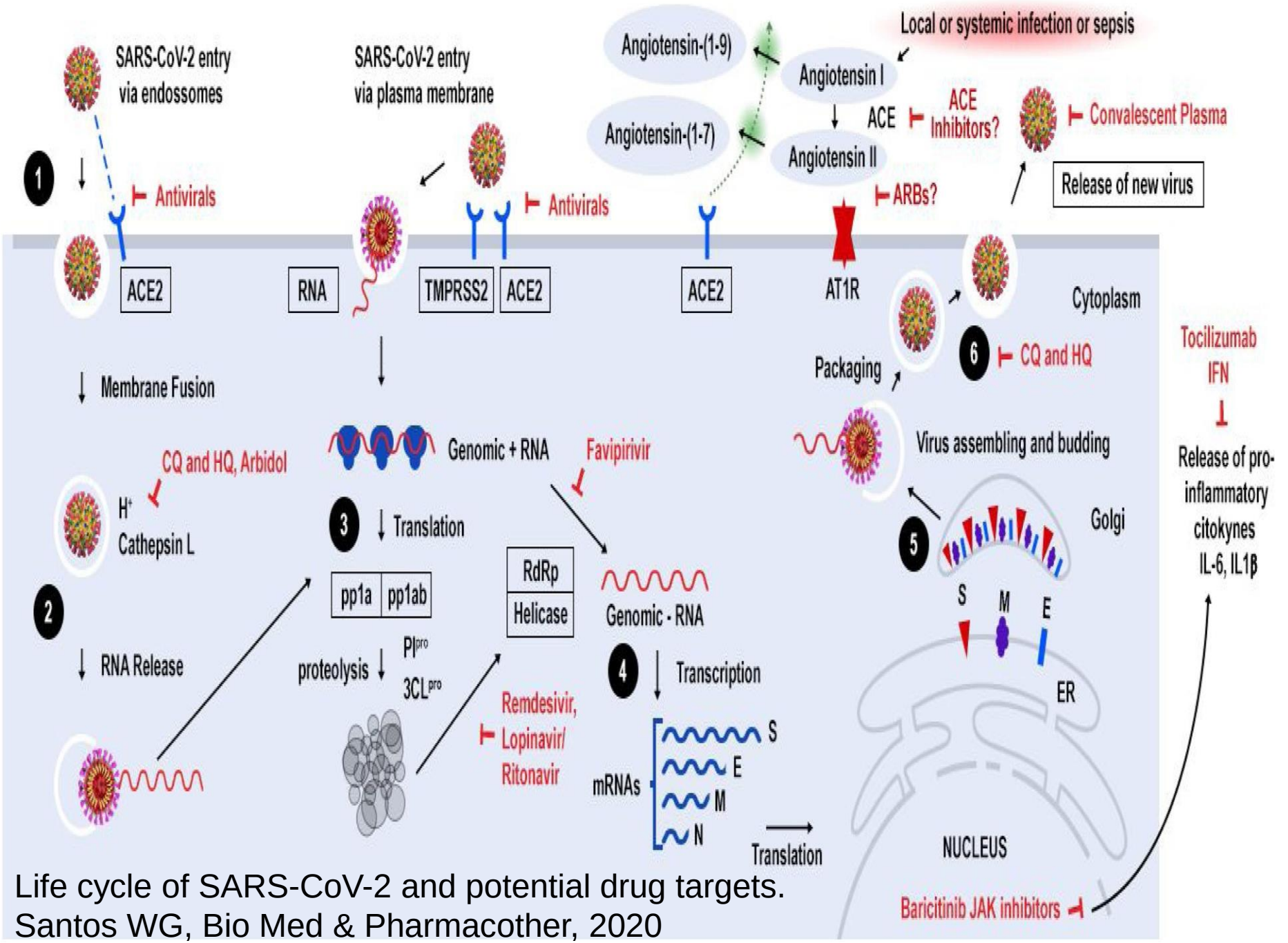
Garden of Knowledge and Virtue

IMMUNISATION ADVOCACY CHAPTER

Highlights:

- Explain life cycle of SARS-CoV-2 and potential drug targets.
- Discuss information regarding antivirals for Covid-19.

Disclaimer: No conflict of interest to declare.



Life cycle of SARS-CoV-2 and potential drug targets.
Santos WG, Bio Med & Pharmacother, 2020

The possible modes of action of anti-viral agents:

1. Inactivate extracellular virus particles.
2. Prevent viral attachment and/or entry.
3. Prevent replication of the viral genome.
4. Prevent synthesis of specific viral protein(s).
5. Prevent assembly or release of new infectious virions

Zaidi, A.K., Dehgani-Mobaraki, P. *J Antiobiot (2021)*
https://doi.org/10.1038/s41429-021-00430-5

- Remdesivir, favipiravir
- Lopinavir/Ritonavir and Other HIV Protease Inhibitors
- Chloroquine or Hydroxychloroquine With or Without Azithromycin
- Ivermectin
- Others

Antiviral	Mechanism of action	Recommended dosing regimen	Contraindication	Adverse effects	Drug interactions
RNA–dependent RNA polymerase (RdRP) inhibitor					
Favipiravir	Pyrazinecarboxamide derivative that mimics purines or purine nucleosides and selectively inhibits RNA-dependent RNA polymerase of RNA viruses during viral replication. Favipiravir showed promising *in vitro* antiviral activities against various RNA viruses, including influenza virus, West Nile virus, Ebola virus, yellow fever virus, and Chikungunya virus. It was approved in Japan in 2014 to treat novel or re-emerging pandemic influenza virus infection when other antiviral drugs are ineffective.	A higher end of the dosing range using a loading dose of 2400 mg to 3000 mg every 12 h x 2 doses followed by a maintenance dose of 1200 mg to 1800 mg every 12 h	Pregnancy, breastfeeding	Hyperuricemia, diarrhea, elevated transaminases, decreased neutrophil count, decreased appetite	CYP2C8 and aldehyde oxidase inhibitor Influenza virus vaccine (live/attenuated)
Remdesivir	Adenosine nucleotide analog and inhibitor of RNA-dependent RNA polymerase. Drug was initially developed to treat Ebola and Marburg virus infections. It has demonstrated *in vitro* and *in vivo* activity in animal models against coronaviruses including MERS and SARS.	200 mg loading dose, and 100 mg every 24 h as IV infusion.	Not recommended in patients with GFR < 30	Elevated transaminase, kidney injury, hyperglycemia, fever	Chloroquine, hydroxychloroquine

Antiviral	Mechanism of action	Recommended dosing regimen	Contraindication	Adverse effects	Drug interactions
Protease inhibitor					
ASC-09 (TMC-310911)	Protease inhibitor that is structurally similar to its parent molecule, darunavir. It acts as a peptidomimetic inhibitor and dimerization inhibitor, inhibits the cleavage of polypeptides into functional proteins required for infectious HIV. It is given in combination with ritonavir.	Ritonavir/ASC-09 100 mg/300 mg twice daily	Allergic to components of ASC-09/ritonavir tablet	Fatigue, nausea, gastrointestinal effects, increase in liver enzyme level	Not available
Danoprevir	Hepatitis C virus NS3 protease inhibitor which selectively inhibits HCV replication. It is used in combination with ritonavir. Danoprevir is currently licensed in China for the treatment of chronic hepatitis C, in combination with ritonavir, peg-interferon alpha and ribavirin.	Danoprevir/ritonavir 100/100 mg twice daily	Not available	Neutropenia	Strong inhibitor of CYP3A4
Darunavir	Protease inhibitor which inhibits HIV-1 protease. It selectively inhibits the cleavage of polypeptides in infected cells, thus preventing the formation of mature viral particles. It is used in combination with cobicistat or ritonavir, which are potent inhibitors of CYP3A isozymes, to increase the systemic exposure of protease inhibitor.	Darunavir/cobicistat 800 mg/150 mg once daily	Severe (Child-Pugh Class C) hepatic impairment, co-administration with CYP3A4 inhibitors	Skin rash, increased serum cholesterol, increased serum glucose, gastrointestinal effect, headache, fatigue, increased liver enzymes	Strong inhibitor and inducer of CYP3A4
Lopinavir/ritonavir	HIV protease inhibitor which selectively inhibits the cleavage of polypeptides in infected cells, thus preventing the formation of mature viral particles. Ritonavir is mainly used to enhance the action of protease inhibitor by inhibition of CYP3A4 isozymes.	400 mg/100 mg every 12 h for up to 14 days	Hypersensitivity, co-administration with CYP3A4 inducer or inhibitor	Gastrointestinal intolerance, nausea, vomiting, diarrhea, pancreatitis, hepatotoxicity, cardiac conduct abnormalities	Inducers and inhibitors of CYP3A4

Antiviral	Mechanism of action	Recommended dosing regimen	Contraindication	Adverse effects	Drug interactions
Nucleoside inhibitor					
Azvudine	Azidocytidine nucleoside analog and nucleoside reverse transcriptase inhibitor. It is metabolized intracellularly into active triphosphate form and incorporates into primer strand by reverse transcriptase, resulting viral DNA chain termination. It demonstrates antiviral activity on HIV, hepatitis B virus and hepatitis C virus.	Azvudine 10 mg on day 1, then 5 mg once daily on day 2–5	Not available	Not available	Not available
Tenofovir disoproxil fumarate	Adenosine nucleotide analog and inhibitor of RNA-dependent DNA polymerase resulting in inhibition of viral replication. It is approved for treatment of Hepatitis B and HIV-1 infection.	Tenofovir disoproxil fumarate/emtricitabine 245 mg/200 mg daily	Hypersensitivity	Pruritus, increased serum lipid, gastrointestinal effect, insomnia, pain, dizziness, depression, decreased bone mineral density	Cidofovir, lopinavir/ritonavir, didanosine, atazanavir
Ribavirin	Guanosine nucleoside analog and inhibitor of virus RNA polymerase activity. It is indicated for treatment of chronic hepatitis C virus infection.	500–600 mg twice daily	Pregnancy, hemoglobinopathies, concomitant use with didanosine, CrCl < 50 mL/min	Fatigue, pyrexia, myalgia, headache, depression, hepatic decompensation	Nucleoside analogs, azathioprine
Neuroamidase inhibitor					
Oseltamivir	Potent inhibitor of influenza virus neuraminidase enzymes found on the surface of the virus, which prevents budding from the host cell, viral replication, and infectivity. It is currently licensed for used in the treatment and prophylaxis of infection with influenza viruses A (including pandemic H1N1) and influenza B.	75 mg twice daily	Hypersensitivity to oseltamivir or component of the formulation, not recommended in ESRD not undergoing dialysis	Gastrointestinal effect, headache, pain	Dichlorphenamide, probenecid, influenza virus vaccine (live/attenuated)

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Polymerase acidic endonuclease inhibitors					
Baloxavir Marboxil	Selective inhibitor of influenza cap-dependent endonuclease thus preventing polymerase function and influenza virus mRNA replication. The drug is currently approved for treatment of influenza virus A and B.	80 mg on day 1, day 4 and day 7 (no more than 3 doses)	Hypersensitivity	Diarrhea, bronchitis, nausea, sinusitis, headache	Polyvalent cation-containing laxatives, antacids or oral supplements Live attenuated influenza

Last Updated: April 21, 2021

https://www.covid19treatmentguidelines.nih.gov/tables/table-2d/

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir				
For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) *For Patients Who Are Not Mechanically Ventilated and/or on ECMO:* • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5 • Treatment may be extended to up to 10 days in patients who do not show clinical improvement after 5 days of therapy. *For Mechanically Ventilated Patients and/or Patients on ECMO:* • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD. • Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.	• Infusion reactions • Renal function, hepatic function, and prothrombin time should be monitored before and during treatment as clinically indicated. • RDV **is not recommended** if eGFR is <30 mL/min. • RDV may need to be discontinued if ALT level increases to >10 times the ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.[1]	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[1] • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.[1] • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUA[a] is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. • A list of clinical trials is available here: Remdesivir

Cochrane Library

Cochrane Database of Systematic Reviews

Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19 (Review)

Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T

Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD013587. DOI: 10.1002/14651858.CD013587.pub2. Accessed 22 June 2021.

- Hydroxychloroquine (HCQ) has no clinical benefit in treating COVID-19 in hospitalized patients, with moderate- to high-certainty evidence from several randomized trials, and a probable increase in adverse events associated with its use.
- Evidence for prevention of hospital admission in outpatients with COVID-19 is very uncertain.
- Given the lack of benefit in hospitalized patients, and limited available evidence suggesting little or no effect on clearance of the virus from the respiratory tract, benefit from treatment of outpatients appears unlikely.

- The lack of any demonstrable clinical benefit in the treatment of COVID-19 makes it less likely the drug will prevent the illness in those who are exposed.
- No trials of the use of HCQ for prophylaxis of COVID-19 in those at risk of exposure to SARS-CoV-2 were identified.
- Evidence that HCQ is effective as prophylaxis for COVID-19 in people exposed to SARS-CoV-2 is limited.
- HCQ probably increases adverse events, although there does not appear to be a difference between comparison groups for serious adverse events.

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

WHO Solidarity Trial Consortium*

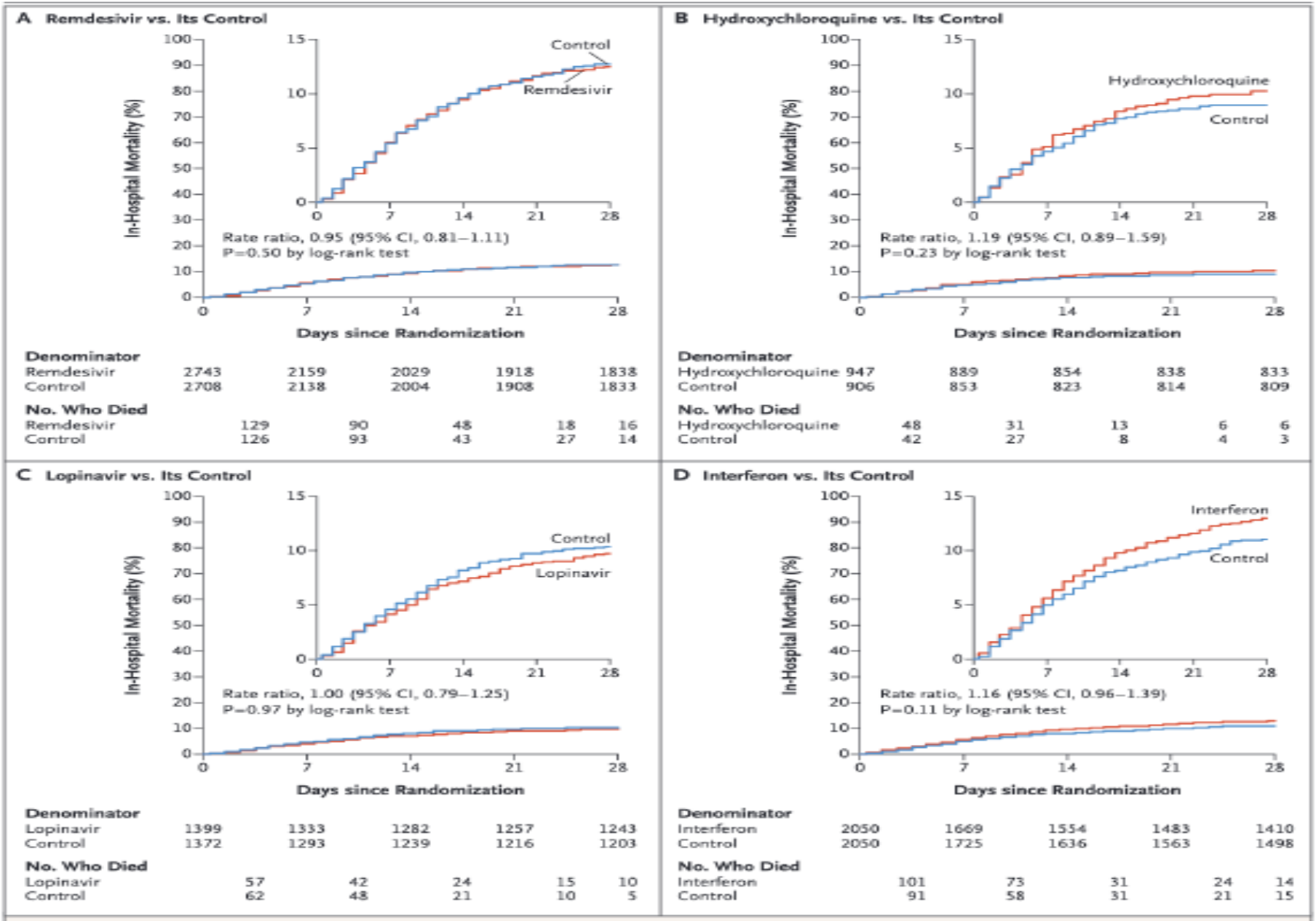
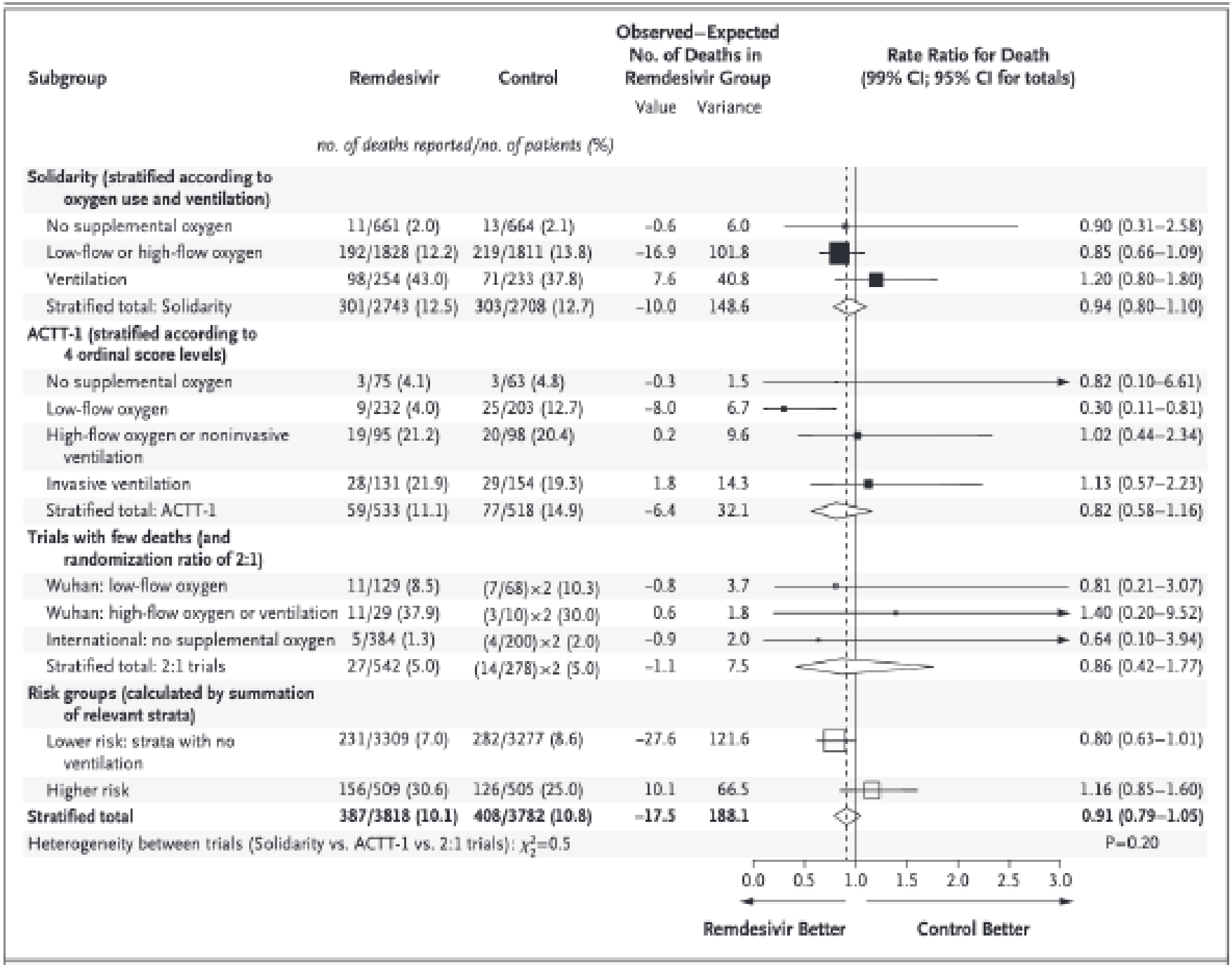


Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.


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
0.0 0.5 1.0 1.5 2.0 2.5 3.0
Remdesivir Better
Control Better

CLINICAL MANAGEMENT OF CONFIRMED COVID-19 CASE IN ADULT AND PAEDIATRIC

Table 2: Specific treatment of COVID-19 disease

Category	Treatment
1	No treatment required
2	No treatment required • Close observation of vital signs and oxygen saturation as stated in monitoring guidelines. Look for warning signs at each review.
3	Generally, no treatment required • Close observation of vital signs and oxygen saturation as stated in monitoring guidelines. • Treat with Favipiravir as category 4 if patient has any of the following risk factors: o Age ≥ 50years with co-morbid o ESRF (consult ID physician on the choice of treatment) o In the presence of any warning signs (see below)

4

- **A) Antiviral treatment**

Drug	Dose & Duration	Comments
Favipiravir	1800mg bd for 1 day then 800mg bd 5 days Optimal duration of antiviral treatment is unknown. A study on Remdesivir showed no difference between 5 day and 10 day course of treatment (JAMA. doi:10.1001/jama.2020.16349) Antivirals have not shown to be effective when initiated in hyper inflammatory phase of disease (see figure below). Consider stopping or not initiating the drug in hyperinflammatory phase of the disease.	Teratogenic effect: Favipiravir is contraindicated for women of childbearing potential and men whose partner is of childbearing potential. In this group, if Favipiravir is used, they should be advised to use contraception for 7 days after the last dose of Favipiravir Avoid if GFR <30ml/min Consult ID physician for usage in ESRF patients on regular dialysis. Common side effects: • Hyperuricemia • Diarrhoea • Elevated transaminase • Neutropenia Drug interactions: • Paracetamol – maximum 3gm per day • Theophylline – increases Favipiravir levels • Pyrazinamide – both cause hyperuricemia

http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_2e_CLINICAL_MANAGEMENT_OF_CONFIRMED_COVID-19_CASE_IN_ADULT_AND_PEADIATRICS-03052021.pdf

IVERMECTIN

Zaidi, A.K., Dehgani-Mobaraki, P. *J Antibiot* (2021)

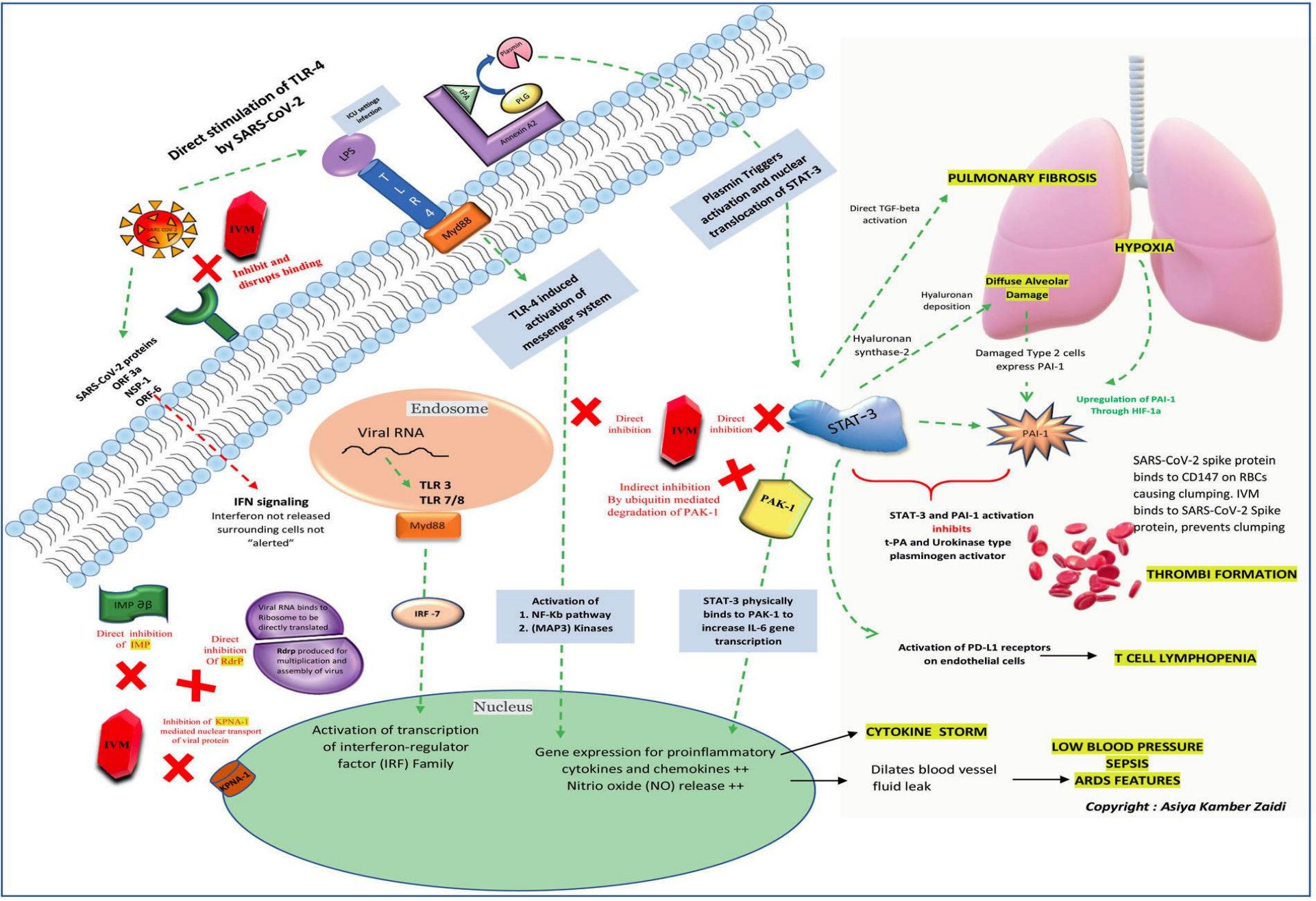


Table 1 All 55 ivermectin COVID-19 trials (As per data available on 16 May 2021) divided based on stage of treatment (Early Vs Late) and the type of study

Study	Study Type
EARLY TREATMENT	
Random effects meta-analysis with pooled effects showed 79% improvement for early treatment RR 0.21 and CI [0.11-0.37]	
Double-Blind Randomized controlled trial	Mahmud et al.*, Ahmed et al.*, Chaccour et al.*, Babalola et al.*, Kirti et al., Mohan et al., Schwartz et al., Lopez- Medina et al.*, Chahla et al.
Single-blind Randomized controlled trial	Raad et al.
Randomized controlled trial	Bukhari et al., Chowdhury et al.*, Faisal et al.*
Retrospective quasi-randomized study	Loue et al*, Merino et al
Other studies	Espitia-Hernandez et al.*, Carvallo et al., Cadegiani et al., Afsar et al., Elalfy et al.*, Roy et al., Mourya et al.*
LATE TREATMENT	
Random effects meta-analysis with pooled effects showed 46% improvement for late treatment RR 0.54 and CI [0.40-0.72]	
Randomized controlled trial	Kishoria et al.*, Podder et al.*, Chachar et al.*, Elgazzar et al.. Pott-Junior et al.*
Double-Blind Randomized controlled trial	Niaee et al.,Okumus et al.*, Shahbazn et al.*, Gonzalez et al.*. Huvenek et al.
Single-Blind Randomized controlled trial	Hashim et al.
Other studies	Gorial et al., Khan et al., Soto-Becerra et al, Rajter et al.*, Camprubi et al.*, Spoorthi et al*, Budhiraja et al., Lima Morales et al.*

Comments (1)

Molnupiravir, an Oral Antiviral Treatment for COVID-19

William Fischer, Joseph J. Eron Jr, Wayne Holman, Myron S. Cohen, Lei Fang, Laura J. Szewczyk, Timothy P Sheahan, Ralph Baric, Katie R. Mollan, Cameron R. Wolfe, Elizabeth R. Duke, Masoud M. Azizad, Katyna Borroto-Esoda, David A. Wohl, Amy James Loftis, Paul Alabanza, Felicia Lipansky, Wendy P. Painter

doi: https://doi.org/10.1101/2021.06.17.21258639

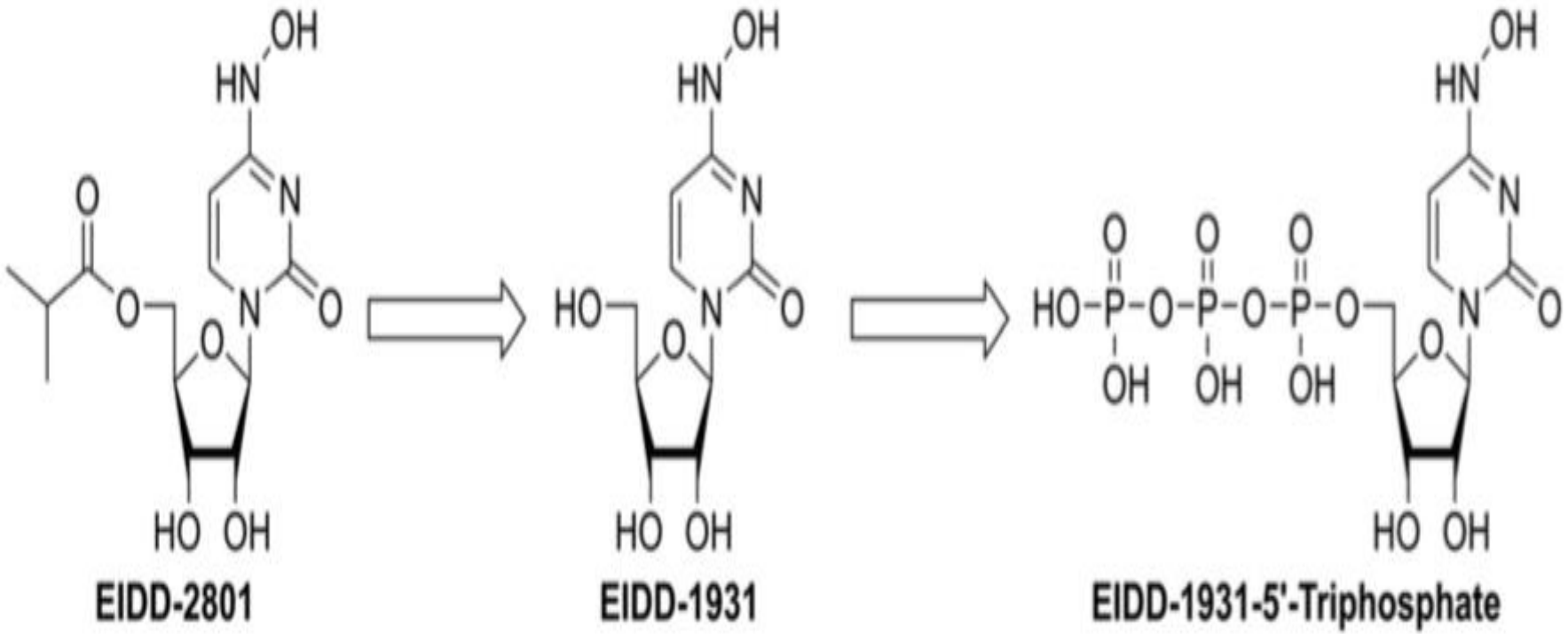


FIG 1 Molnupiravir is rapidly converted in the plasma to EIDD-1931 (NHC), which after distribution into various tissues is converted by host kinases into EIDD-1931 5′-triphosphate, the active antiviral agent.

- Phase 2a trial evaluating the safety, tolerability, and antiviral efficacy of molnupiravir in the treatment of COVID-19.
- Among 202 treated participants, virus isolation was significantly lower in participants receiving 800 mg molnupiravir (1.9%) versus placebo (16.7%) at Day 3

  ($p = 0.02$).
- At Day 5, virus was not isolated from any participants receiving 400 or 800 mg molnupiravir, versus 11.1% of those receiving placebo ($p = 0.03$).
- Time to viral RNA clearance was decreased and a greater proportion overall achieved clearance in participants administered 800 mg molnupiravir versus placebo

  ($p = 0.01$).
- Molnupiravir was generally well tolerated, with similar numbers of adverse events across all groups (HA, diarrhea).

- A randomized, double-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study in healthy adults evaluating the safety, tolerability and pharmacokinetics of PF-07321332, an oral antiviral protease inhibitor reported having potent antiviral activity in vitro against SARS-CoV-2.
- Phase I trial just started March 2021.
- PF-07304814, IV protease inhibitor, Phase 1b multi-dose trial in hospitalized clinical trial participants with COVID-19.

SUMMARY

- Ongoing research and pharmacovigilance on antivirals for Covid-19 management.
- Antivirals for prevention and treatment, to be used at home by people who test positive for SARS-CoV-2 infection, to stop the virus spreading and speed up recovery time.
- Pharmacists can apply power of knowledge on antiviral drugs to ensure good quality data on effectiveness and safety of COVID-19 management.

THANK YOU

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