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**TENNESSEE**  
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# **Current and Future Treatments for COVID-19**

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## Disclosures

- **I have received funding or served on an advising council for the following entities:**
  - Paratek Pharmaceuticals
  - Cumberland Pharmaceuticals
  - Summit Therapeutics
- **There are no Food and Drug Administration-approved therapies for treatment of COVID-19.**

## **Objectives**

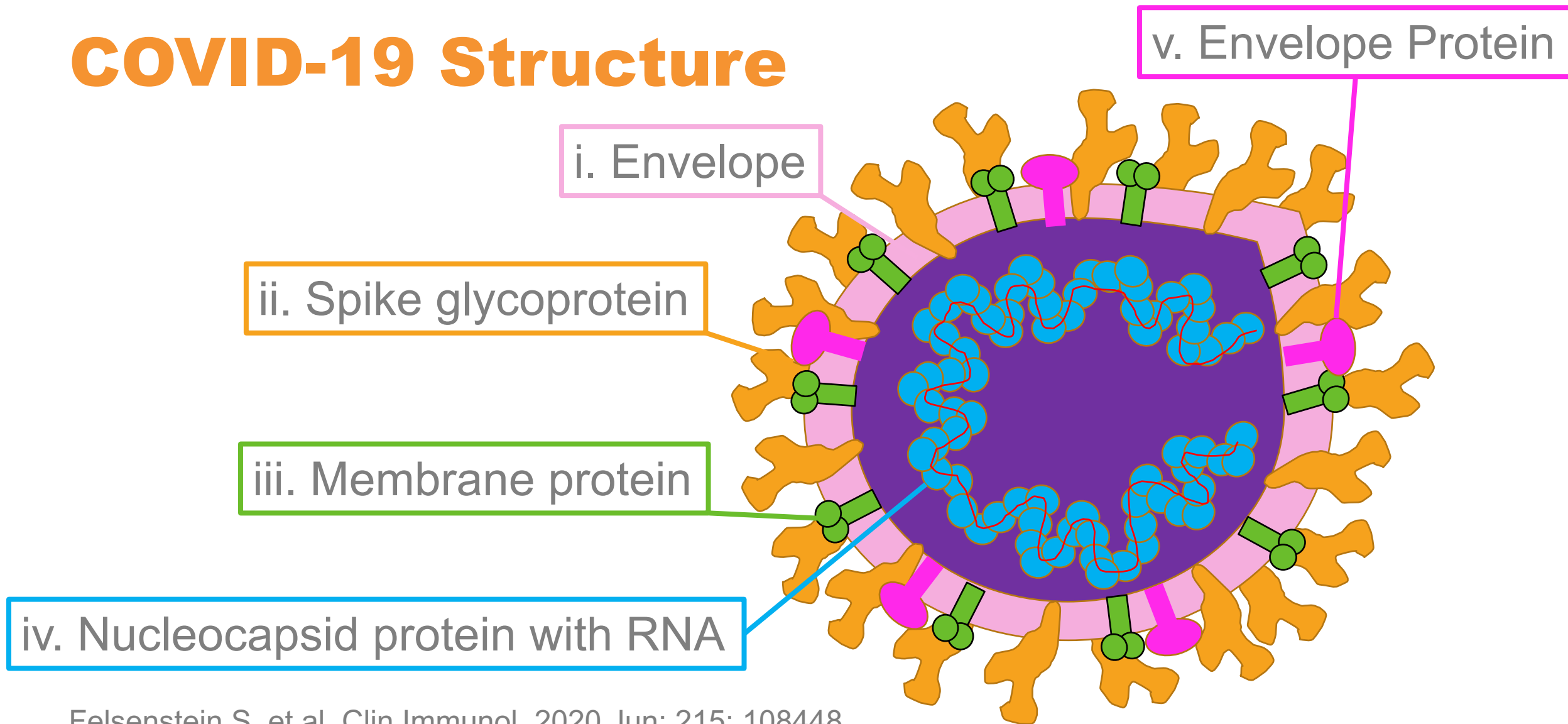
- i. Identify therapies currently explored as treatment options in COVID-19.**
  
- ii. Understand some of the literature supporting or refuting these treatment options for COVID-19.**

# Coronavirus Disease 2019: A Public Health Pandemic

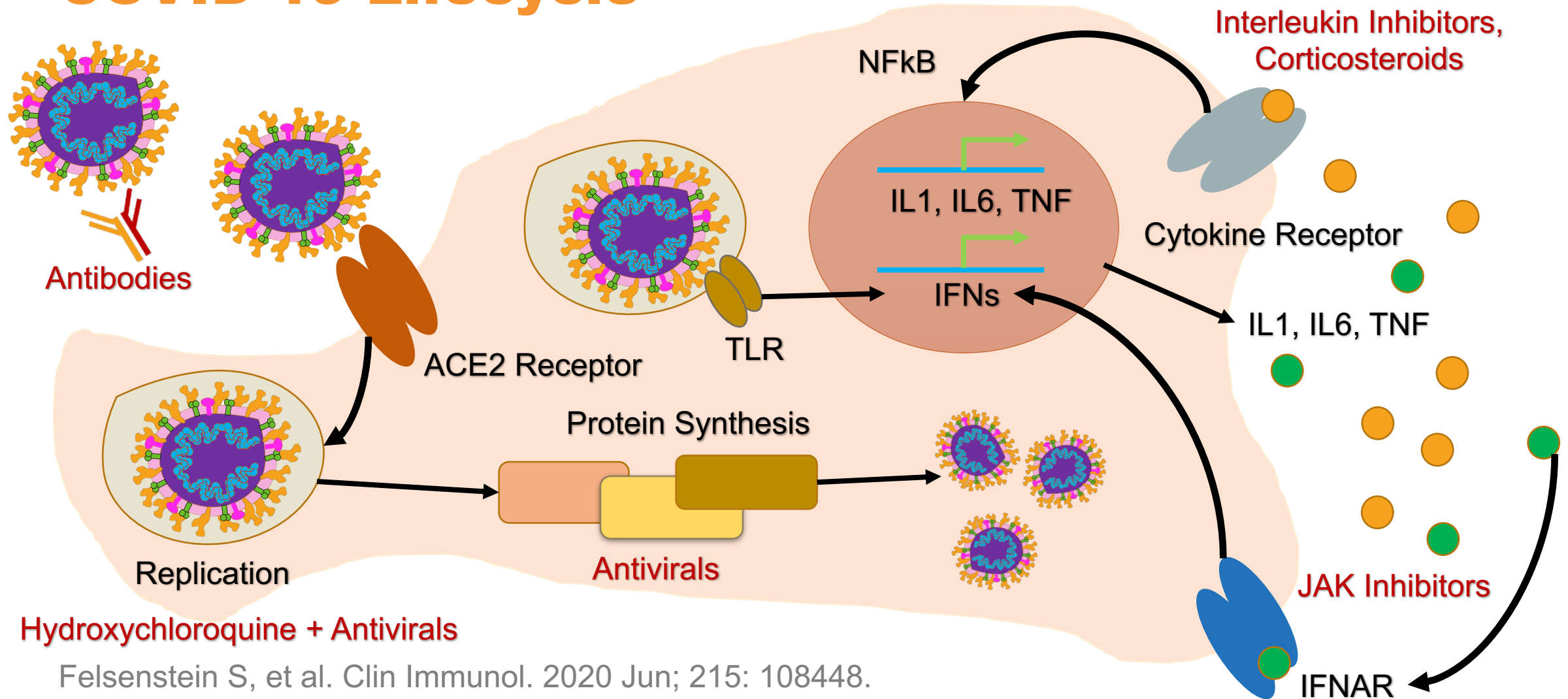
- **United States = Highest cases/death**
- **Progression to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)**
  - Low O<sub>2</sub> saturation, mechanical ventilation, extracorporeal membrane oxygenation
- **Several currently available drugs repurposed**

World Health Organization Coronavirus Disease (COVID-19) Dashboard. Available at <https://covid19.who.int/>. Accessed [Sept 2020]; COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [Sept 2020].

# COVID-19 Structure

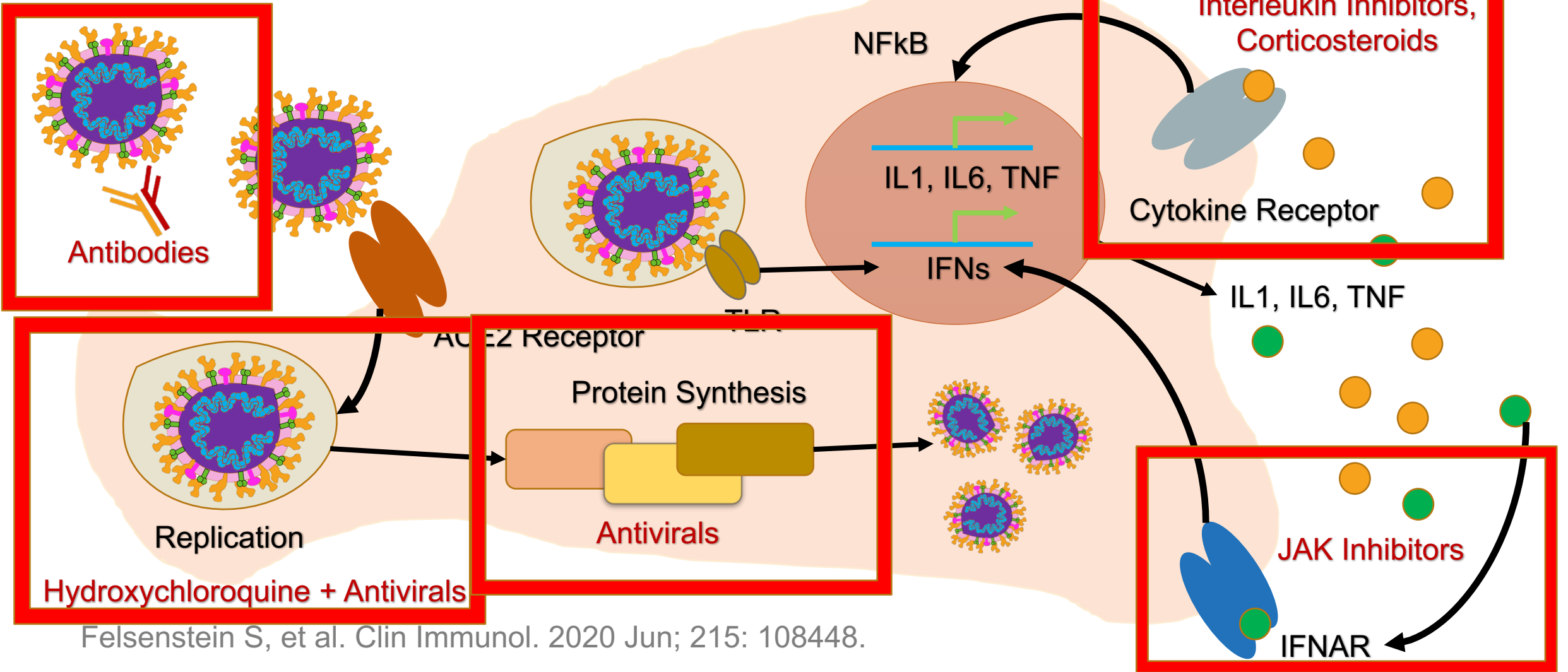


# COVID-19 Lifecycle



**Hydroxychloroquine + Antivirals**

# COVID-19 Lifecycle



Felsenstein S, et al. Clin Immunol. 2020 Jun; 215: 108448.

# **“Promising\* Therapies” in COVID-19**

\*Emphasized caution on the word promising



# Remdesivir (GS-5734)

- **Mechanism:**

- Interferes with viral RNA-dependent RNA polymerase; delayed chain termination of viral RNA transcription

- **Dosing and Pharmacokinetics**

- 200mg IV x1, then 100mg IV daily for 5-10 days
  - Variable renal elimination, 12% protein bound

- **Safety Outcomes**

- CYP interactions?, AST/ALT increases

Emergency Use  
Authorization (EUA) for  
Acute Care Facilities

# Major Remdesivir Clinical Trials



| Characteristics                              | Lancet Severe RCT        |         | ACTT-1                             |          | SIMPLE-1 Severe    |          | SIMPLE-2 Moderate      |          |          |
|--|--------------------------|---------|------------------------------------|----------|--------------------|----------|------------------------|----------|----------|
| <b>Sample, (n)</b>                           | 237                      |         | 1063                               |          | 397                |          | 596                    |          |          |
| <b>Severity</b>                              | Hypoxia, PNA or P/F <300 |         | Hypoxia/PNA/ Suppl' O <sub>2</sub> |          | PNA/Hypoxia, No MV |          | SpO <sub>2</sub> ≥ 94% |          |          |
| <b>Sx duration, days (IQR)</b>               | 10 (9-12)                |         | 9 (6-12)                           | 9 (7-13) | 8 (5-11)           | 9 (6-12) | 8 (5-11)               | 8 (5-11) | 9 (6-11) |
| <b>Intervention</b>                          | 10-day                   | PBO     | 10-day                             | PBO      | 5-day              | 10-day   | 10-day                 | 5-day    | SOC      |
| <b>28-day Mortality, (%)</b>                 | 14                       | 13      | 7.1                                | 11.9     | 8                  | 11       | 3 (2)                  | 2 (1)    | 4 (2)    |
| <b>TTCR (days) / Recovery (%)</b>            | 21 days                  | 23 days | 11 days                            | 15 days  | 10                 | 11       | 7 (4-12)               | 6 (4-9)  | 7 (4-14) |
| <b>AEs &amp; Discontinued Therapy, n (%)</b> | 18 (12)                  | 4 (5)   | 36 (6.7)                           | 36 (6.9) | 9 (5)              | 20 (10)  | 8 (4)                  | 4 (2)    | N/A      |

Key: Sx, symptoms; TTCR, time to clinical recovery; AE, adverse event; PNA, pneumonia; P/F, arterial oxygen partial pressure to fractional inspired oxygen; PBO, placebo; MV, mechanical ventilation; SpO<sub>2</sub>, oxygen saturation; SOC, standard of care; N/A, not applicable

## Summary: Remdesivir

- **Clinical trial data conflicting to date**
  - Reduced time to clinical recovery, questionable mortality data
  - Selection bias, confusing endpoints, underpowered studies
- **Theoretical benefit early in disease progression**
  - Limited effect as viral replication is maximized
  - At least 8 clinical trials on-going
- **Well-tolerated**

# Convalescent Plasma

- **Mechanism**

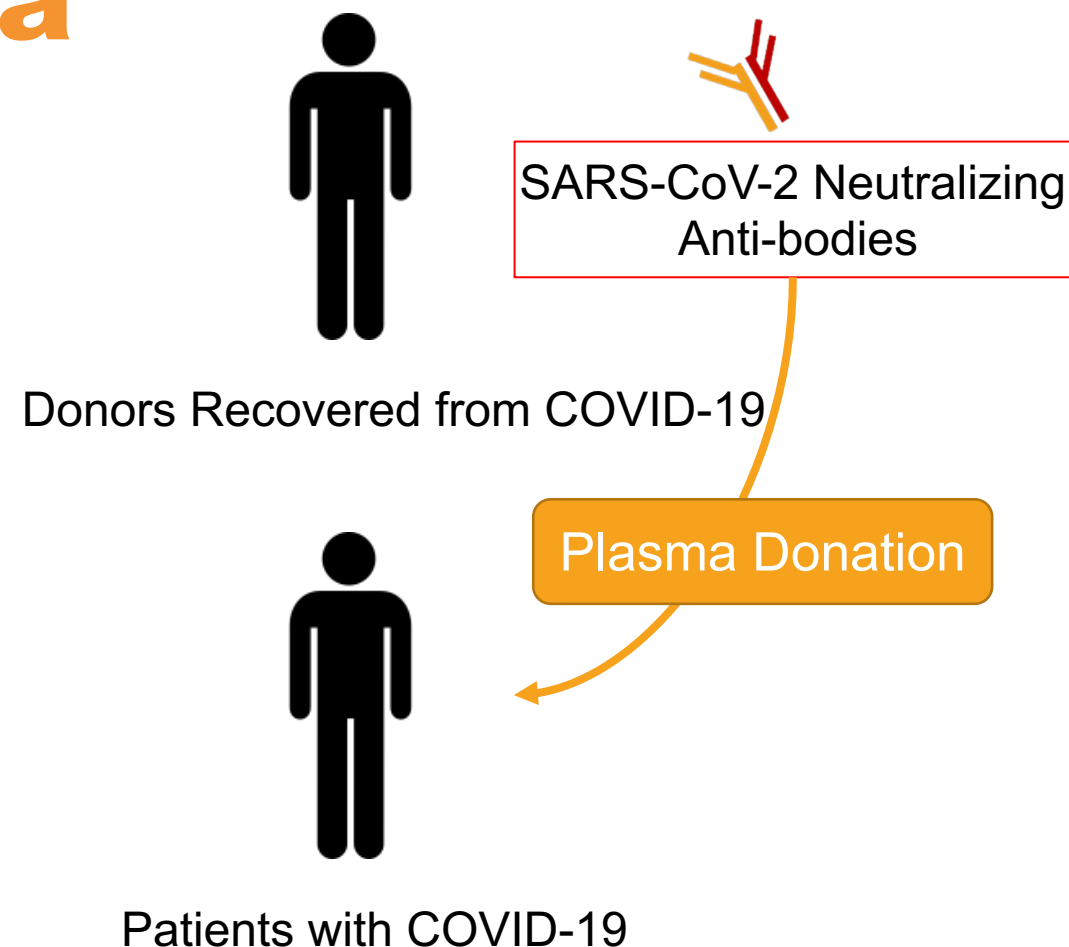
- Adaptive immunity to passive immunity

- **Dosing**

- 1 to 2 units (~200 mL/unit)

- **Contingent on matching**

- Standardization of donor pool
- Adverse effect profile?



# Major Clinical Trial: Convalescent Plasma

- **PLACID Trial**

- Multicenter, randomized Phase II trial
- Hospitalized, moderately ill COVID-19 + patients
- SOC ( $n=235$ ) vs SOC + convalescent plasma x two doses ( $n=229$ )

- **No association with disease progression OR 28-day mortality**

- 17.9% SOC, 18.7% SOC + convalescent plasma
- adjOR: 1.09; 95% CI: 0.67, 1.77

# Summary: Convalescent Plasma

- **Unknown clinical benefit**

- Mortality or time to death
- Symptomatic improvement

Cochrane Review of 20  
studies

+

>5400 patients

- **Unclear benefit of second transfusion**

- **No firm recommendations for use**

- Need for donor pool potency

# Corticosteroids

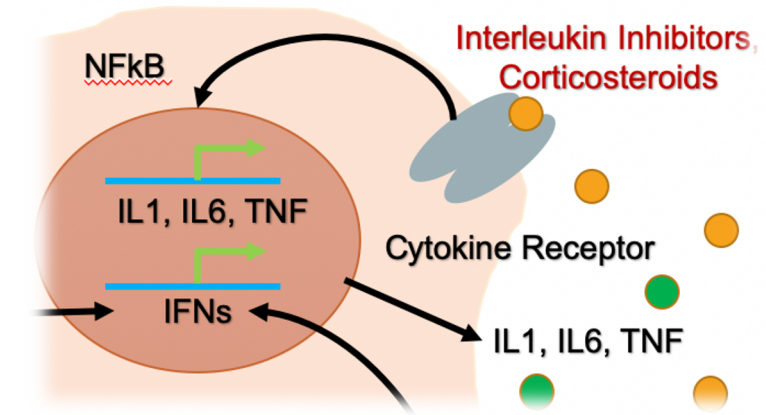
- **Mechanism**

- Anti-inflammatory/immunomodulatory agent
- Reduce pro-inflammatory compounds (i.e., cytokines)

- **Dosage: dexamethasone 6 mg/day for 10 days**

- **Adverse effect profile**

- Potential drug-drug interactions
- Dysglycemia, mood-changes, weight gain



Role in acute respiratory distress syndrome?

# Major Clinical Trial: Corticosteroids

- **RECOVERY Trial**

- Multicenter, open-label adaptive trial in United Kingdom
- Hospitalized, severely ill COVID-19 + patients
- SOC ( $n=4,321$ ) vs SOC + dexamethasone ( $n=6,425$ )
- Very few patients received other anti-COVID therapies

- **Significant reduction in 28-day all-cause mortality**

- 25.7% SOC, 22.9% SOC + dexamethasone
- adjOR: 0.83; 95% CI: 0.75-0.93



# Summary: Corticosteroids

- **Results from RECOVERY suggests mortality benefit in critically ill patients with SARS-CoV-2**
  - Mechanical ventilation or requiring supp'l O<sub>2</sub>
  - No supp'l O<sub>2</sub>, No benefit
- **Several supportive observational studies**
  - Reduced mortality, improved oxygenation, need for mechanical ventilation, hospital or ICU LOS
- **Potentially a class effect?**

**Therapies Lacking Evidence  
for Use in COVID-19**

# Hydroxychloroquine (+/- Azithromycin)

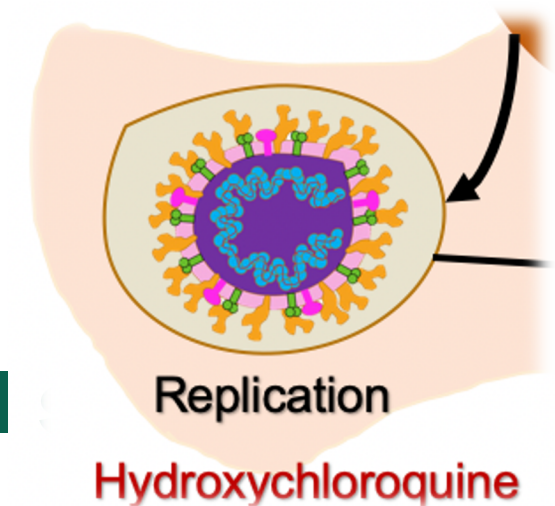
- **Proposed Mechanism:**

- Interference with viral cell entry and replication

- **False inferences from small observational patients**

- **Several conflicting observational data**

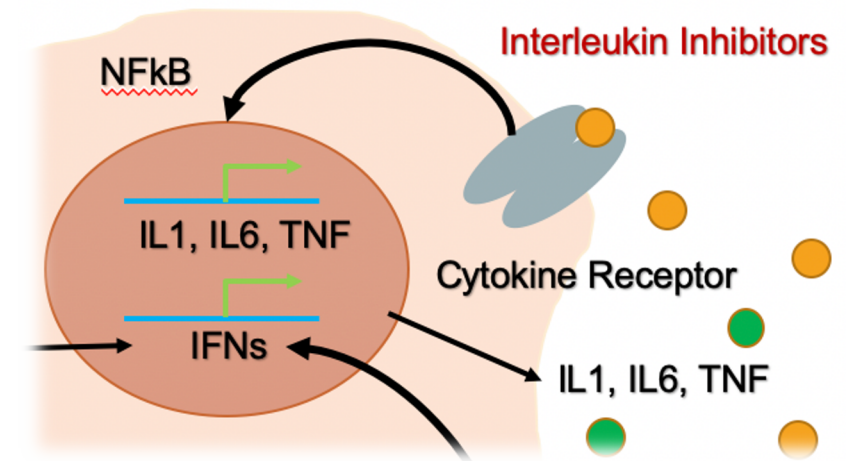
- Henry Ford Hospital data confounded by corticosteroid use



# Interleukin (IL) Inhibitors

- **Tocilizumab, sarilumab, siltuximab**

- Recombinant monoclonal antibodies
- Unclear ideal dosing regimens



- **Potential Role: Cytokine-storm syndrome**

- Adverse events: neutropenia, thrombocytopenia, liver injury

- **Clinical Trials suggest unsuitable for COVID-19 treatment**

- Sarilumab clinical trial failed to meet clinical endpoints

# Therapy-attributed Adverse Effects

- “Do no harm”
- **Cardiac arrhythmias, increased death**
  - QTc prolonging potential
  - Increased with azithromycin
- **Prolonged immunosuppression**
  - Increased risk of secondary infections while hospitalized



# Other Uninspiring COVID-19 Therapies Not Covered in this Presentation

## Other Experimental COVID-19 Therapies

|              |                 |                           |
|--------------|-----------------|---------------------------|
| Ivermectin   | Zinc            | Immunoglobulins           |
| ACEi/ARB     | Oseltamivir     | Baloxovir                 |
| Nitazoxanide | Ribavirin       | Kinase Inhibitors         |
| Interferons  | IL-1 Inhibitors | Other Protease Inhibitors |

**Future Directions for  
COVID-19 Treatment or  
Prevention**

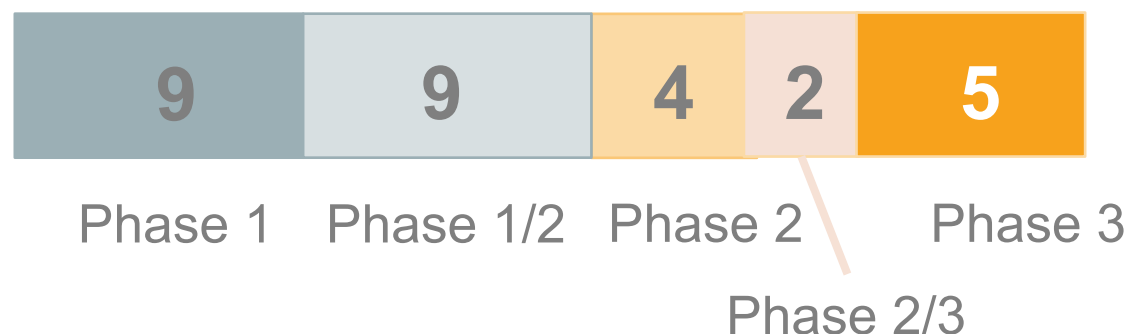
# Favipiravir

- **Mechanism**
  - RNA-dependent RNA polymerase (RdRp) inhibitor
- ***In vivo* data suggest activity towards SARS-CoV-2**
  - Favipiravir ( $n=116$ ) vs umifenovir ( $n=120$ )
  - Higher rate of clinical recovery at 7 days (71% vs 56%)
- **Several RCTs on-going**



# COVID-19 Vaccine Candidates

- 211 vaccine candidates in development
- Successful neutralizing titers for several products



## Notable Phase 2/3:

- Moderna (mRNA-1273)
- Sinopharm (inactivated vaccine)
- Sinovac (CoronaVac)
- Oxford (AZD1222, Phase 2/3)

Data obtained from COVID-19 Live Vaccine Tracker. Available at: <https://www.contagionlive.com/news/the-covid19-live-vaccine-tracker>. Accessed Sept 2020; COVID-19 vaccine tracker. Available at: <https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker>. Accessed Sept 2020.

# Summary: Vaccines in Clinical Trials

- **“When will we get a vaccine”?**
- **Politicization of vaccine/clinical trials**
  - Fast tracking

## **Take Home Points**

- **Bad science has plagued us, too**
- **The jury is still out on some agents, others not so much**
- **Public health/vaccines = better investment in time and resources?**

Looking for more COVID-19 Resources? Visit the Society of Infectious Diseases Pharmacists webpage:  
<https://sidp.org/covid19>



## Other Resources

- **Contagion Live**

- <https://www.contagionlive.com/disease-specific-topics/coronavirus>

- **National Institutes of Health (NIH)**

- <https://www.nih.gov/news-events/news-releases/expert-us-panel-develops-nih-treatment-guidelines-covid-19>

- **Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) guidance**

## **Assessment Question:**

**Which of the following therapies has the highest level of evidence to support a decrease in all-cause mortality for SARS-CoV-2 infections?**

- i. Dexamethasone**
- ii. Convalescent plasma**
- iii. Hydroxychloroquine**
- iv. Remdesivir**



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