COVID-19 Antiviral & Anti-Inflammatory Therapy in Hospitalized Patients: Lessons Learned

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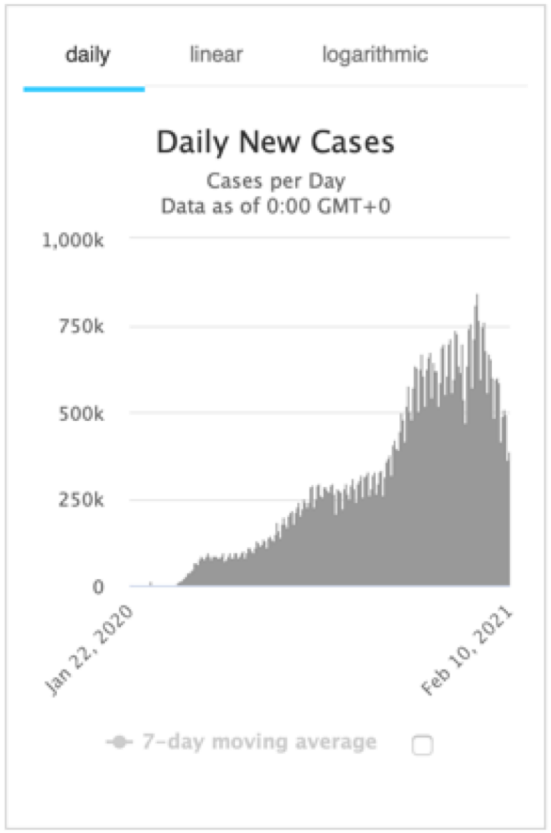
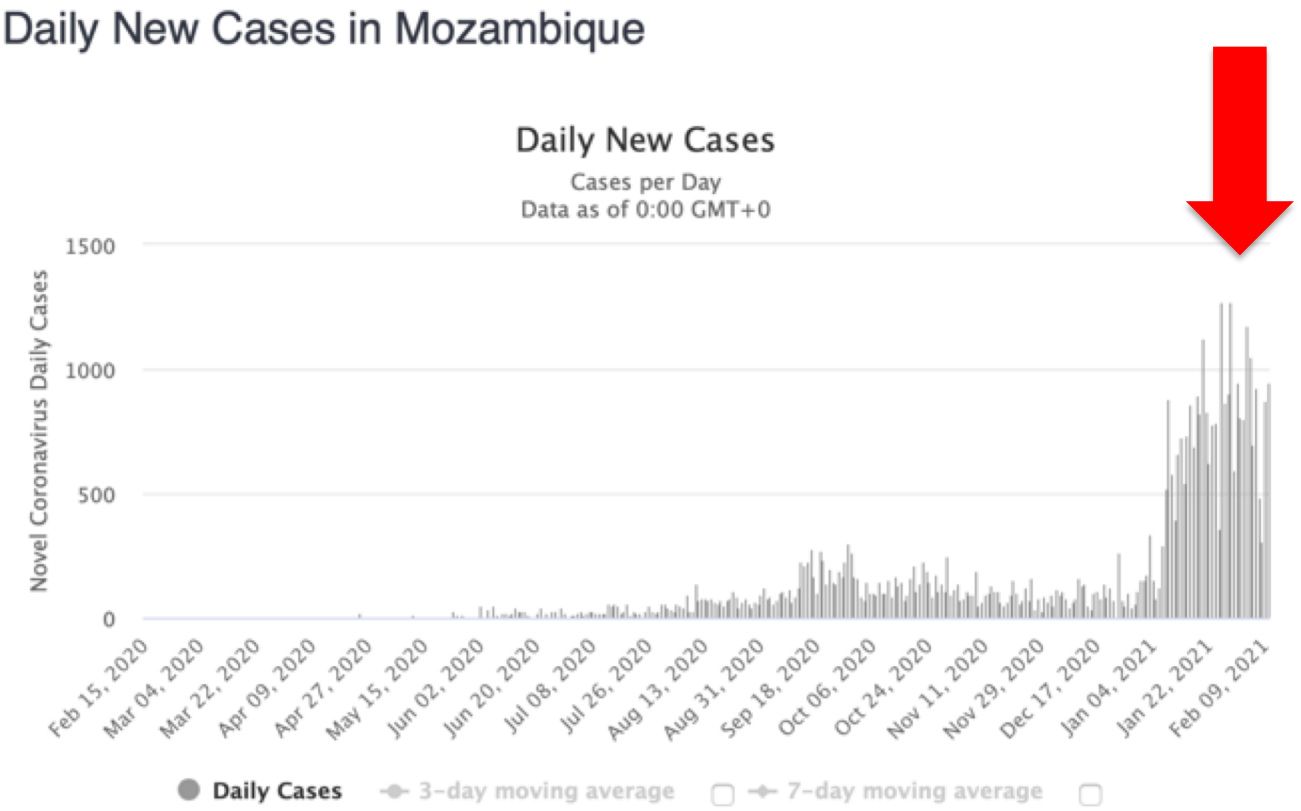
Outline

- Brief Epidemiology Update
- Review of ACTT-1 & other remdesivir antiviral trial results
  - Putting results into clinical context and lessons learned about how to use this antiviral drug
- Anti-inflammatory therapies for COVID-19 pneumonia
  - Dexamethasone, baricitinib and lessons learned
- Making sense of treatment guidelines
- Part 2 will cover other therapies in the outpatient setting

Coronavirus Cases as of February 10, 2021

- Globally, 107,853,095 coronavirus cases
  - 2,364,938 deaths
- Mozambique – 46,736 cases; 486 deaths





Interpreting Therapeutic Response

NIH Guidelines: Defining COVID-19 Disease Severity

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive virologic test for SARS-CoV-2 (ie, NAAT or antigen test) but no symptoms consistent with COVID-19
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste or smell) but no shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$ mm Hg, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

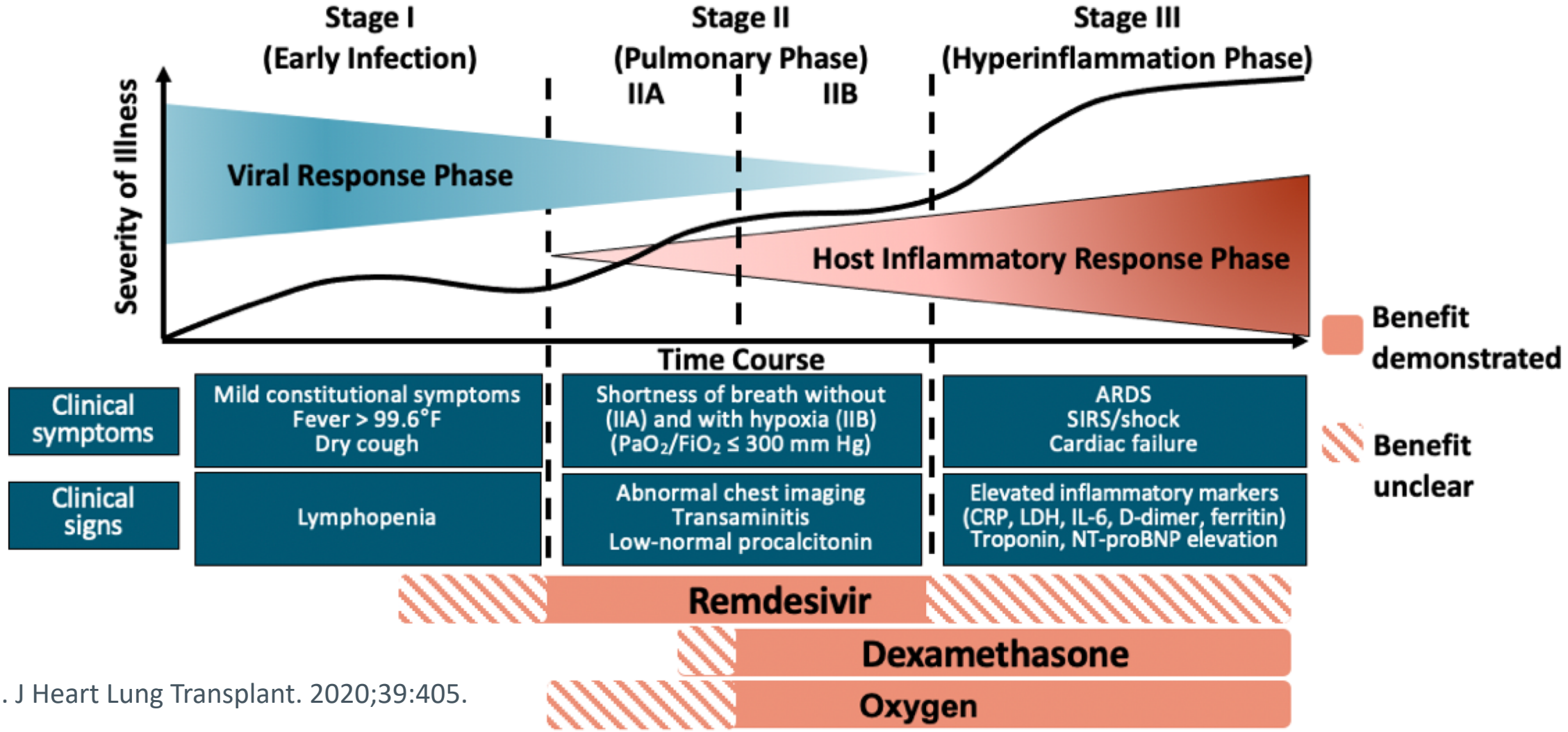
NIH COVID-19 Treatment Guidelines. Clinical spectrum of SARS-CoV-2 infection. Last updated December 17, 2020.

Clinical Trials: Defining COVID-19 Disease Severity

Clinical Severity Based on Ordinal Scale	Clinical Status Description for Assessment
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities, and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen and no longer requires ongoing medical care (if hospitalization extended for infection-control purposes)
4	Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Beigel. NEJM. 2020;383:1813.

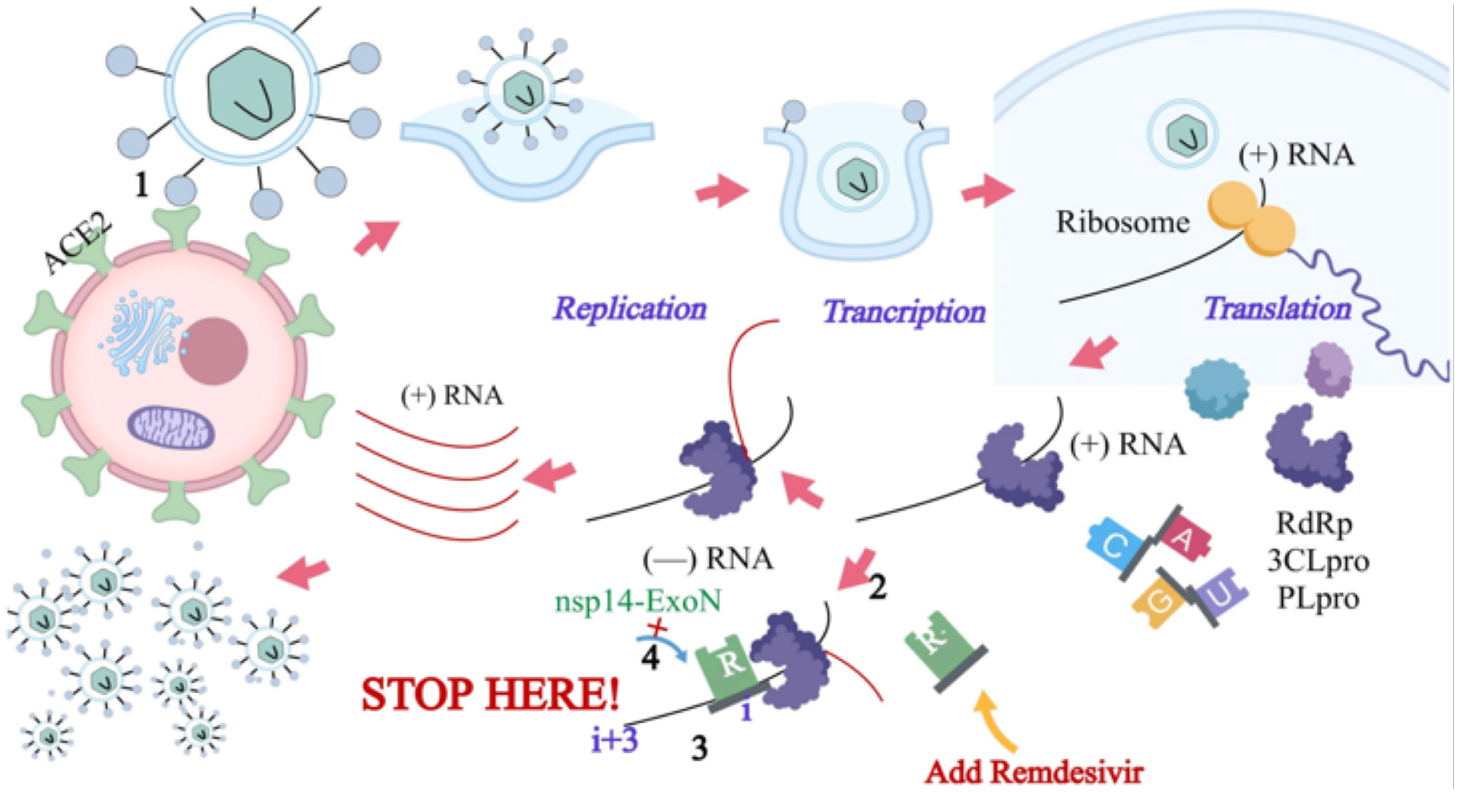
COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Siddiqi. J Heart Lung Transplant. 2020;39:405.

Antiviral Therapy with Remdesivir for Covid-19: Lessons Learned

Remdesivir and the SARS-CoV-2 Replicative Cycle

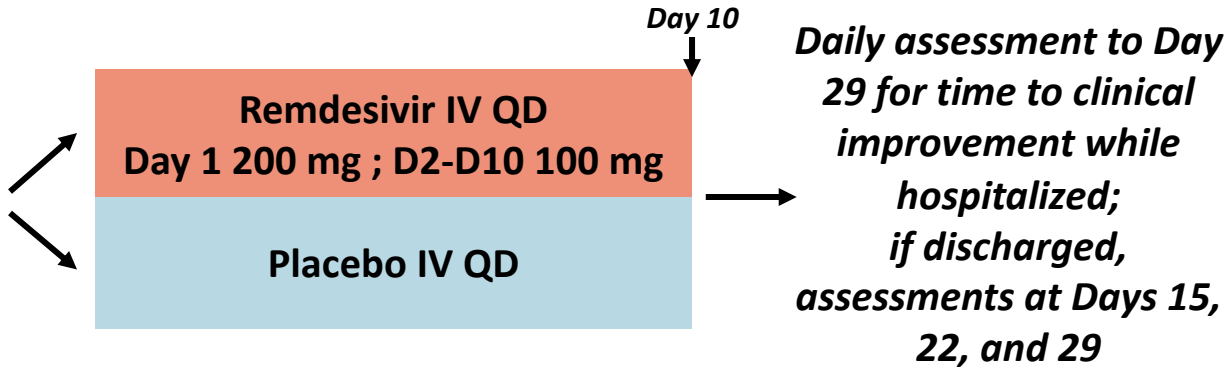


Remdesivir is an RNA-dependent RNA polymerase inhibitor that interferes with viral RNA transcription/translation to interrupt the replicative cycle

Adaptive COVID-19 Treatment Trial (ACTT-1): Study Design

- Multicenter, multinational, adaptive, randomized, double-blind, placebo-controlled phase 3 trial

Adult patients ≥ 18 yrs of age; hospitalized with symptoms of COVID-19/SARS-CoV-2 infection and ≥ 1 of following: radiographic infiltrates; SpO_2 ≤ 94% on room air or requiring supplemental oxygen or or requiring mechanical ventilation (N = 1063)



- Primary endpoint: time to recovery* by Day 29 according to ordinal scale
- Secondary endpoints: treatment-related improvements in 8-point ordinal scale at Day 15

*Day of recovery is first day patient satisfies 1 of these categories from ordinal scale: 1) hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care; 2) not hospitalized, limitation on activities and/or requiring home oxygen; or 3) not hospitalized, no limitations on activities.

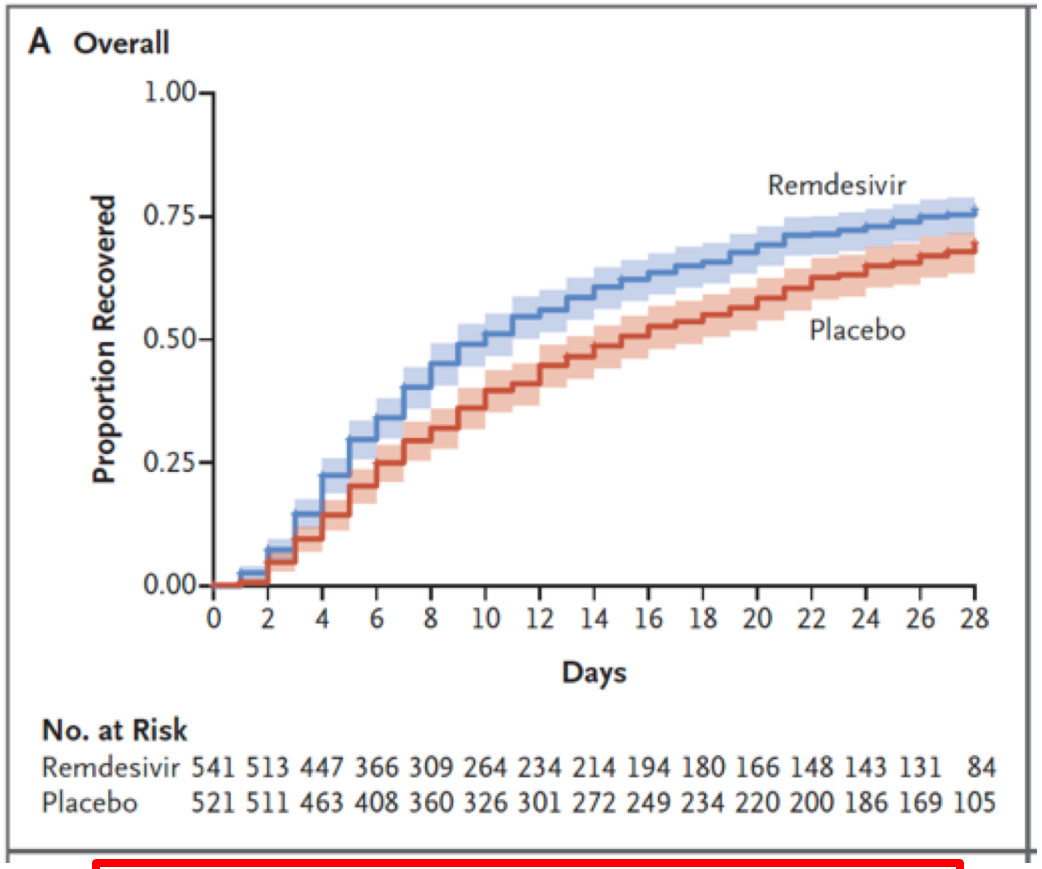
Beigel J, et al. New Engl J Med 2020; [Epub]. NCT04280705

ACTT-1: Endpoints Based on Clinical Status Using the Ordinal Scale

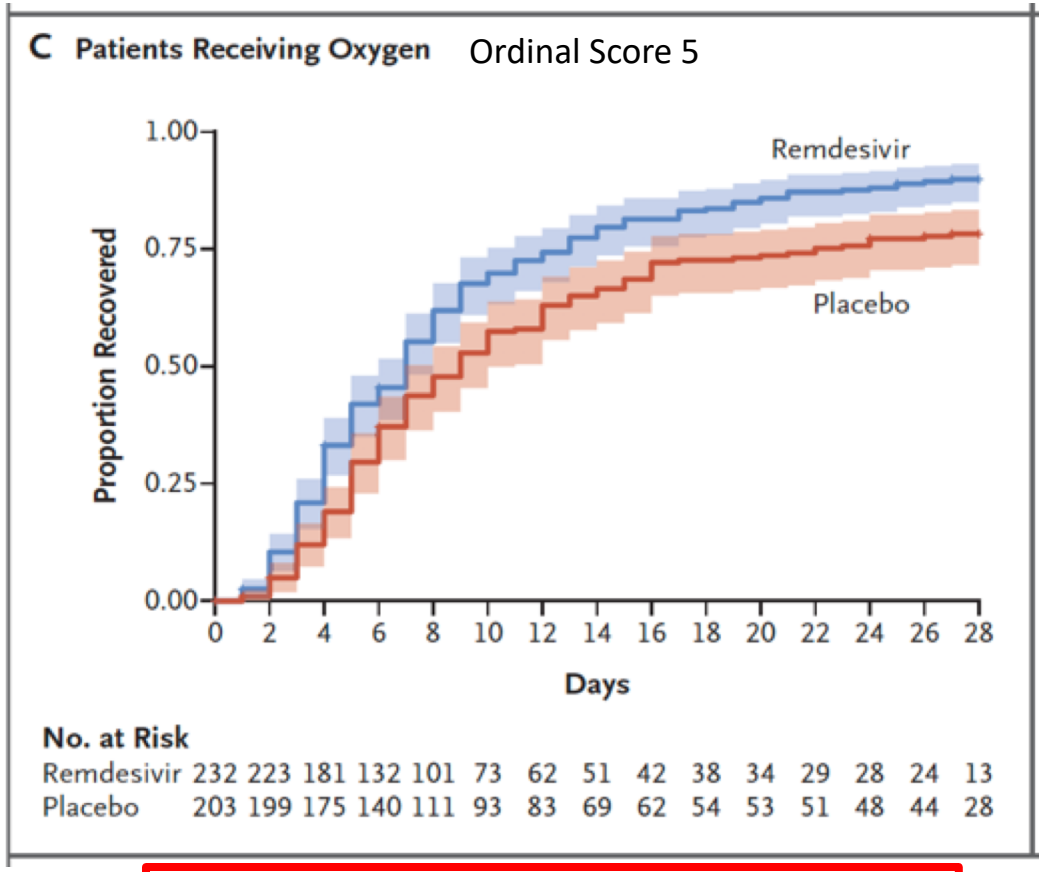
Clinical Status Ordinal Scale	Clinical Status Description for Assessment
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities, and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen and no longer requires ongoing medical care (if hospitalization extended for infection-control purposes)
4	Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

Beigel. NEJM. 2020;383:1813.

Primary Outcome: Shorter Time to Recovery & Reduced Risk of Disease Progression

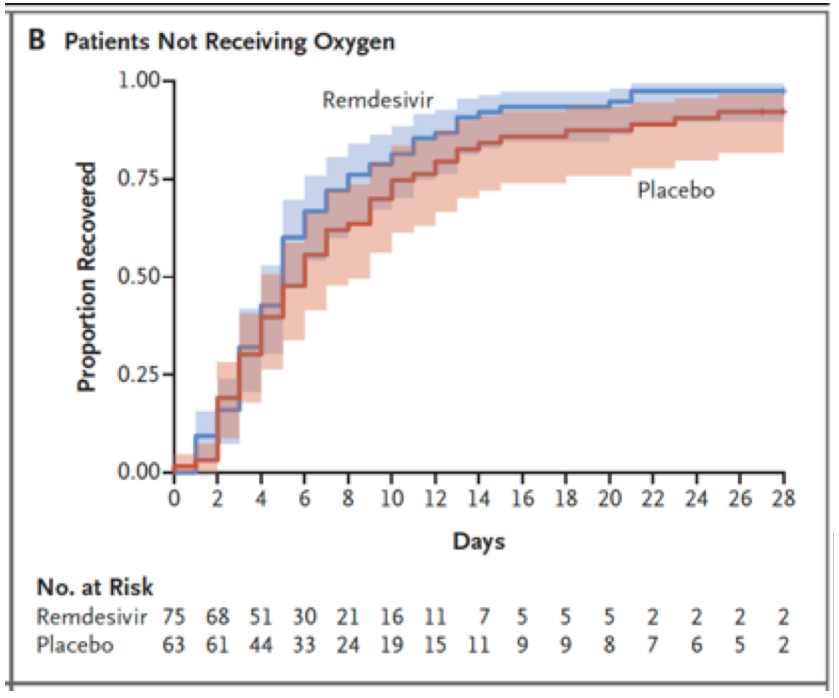


Time to recovery 10 vs 15 days
Rate ratio for recovery 1.29
95% CI, 1.12 to 1.49; p<0.001
Day 29 Mortality 11.4% RDV vs 15.2% Placebo



Time to recovery 11 vs 15 days
Rate ratio for recovery 1.45
95% CI, 1.18 to 1.75; p<0.001
Day 29 Mortality 4.0% RDV vs 12.7% Placebo

Primary Outcome in Key Subgroups: No Significant Improvement



Ordinal Score 4

Rate ratio for recovery 1.29

95% CI, 0.91 to 1.82

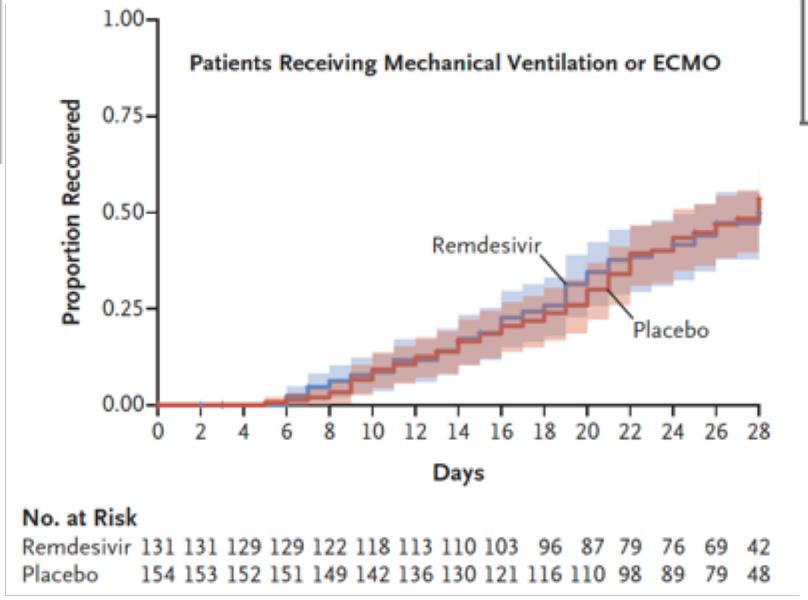
Mortality 4.1% RDV vs 4.8% Placebo

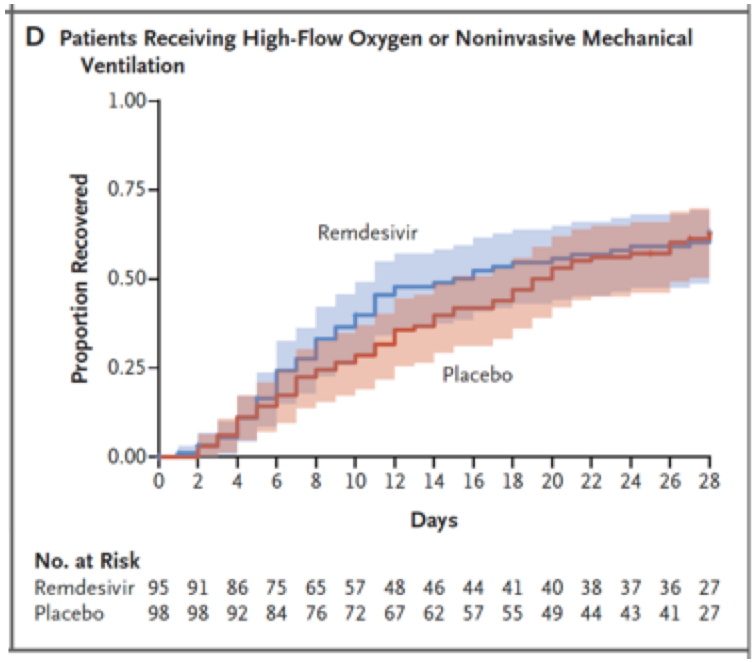
Ordinal Score 7

Rate ratio for recovery 0.98

95% CI, 0.70 to 1.36

Mortality 21.9% RDV vs 19.3% Placebo





Ordinal Score 6

Rate ratio for recovery 1.09

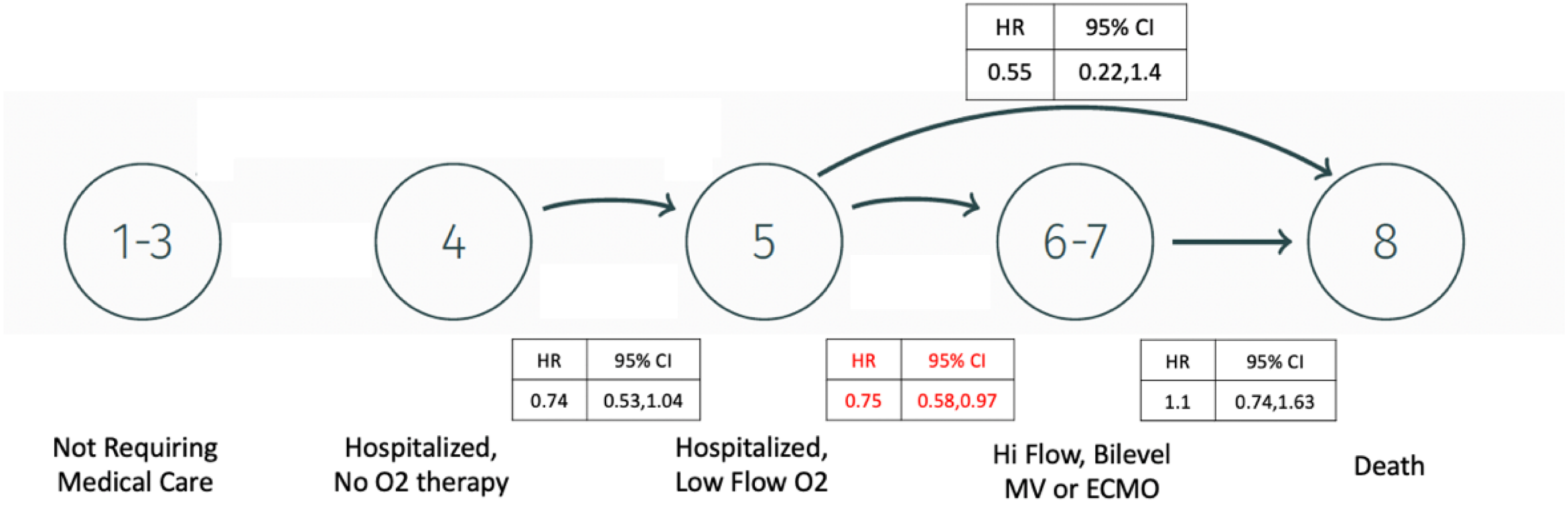
95% CI, 0.76 to 1.57

Mortality 21.2% RDV vs 20.4% Placebo

Beigel JH, et al. NEJM 2020

Remdesivir Reduces the Risk of Clinical Decline

ACTT-1 MARKOV Model by Ordinal Score



Safety of Remdesivir vs Placebo

- Fewer serious adverse events occurred in pts receiving remdesivir (24.6%) compared to placebo (31.6%)
- Most common SAE was respiratory failure; less frequent in the remdesivir group (8.8%) vs the placebo group (15.5%)
- Grade 3 or 4 adverse events occurred less frequently in the remdesivir group (51.3%) than placebo (57.2%)
- Most common non-serious AEs were decreased hemoglobin, decreased eGRF/Cr clearance, increased Cr, hyperglycemia, increased aminotransferases
- No deaths were attributed to study medications

Remdesivir vs Placebo RCT in China

- Randomized, double-blind, placebo-controlled multicenter trial
- 237 pts enrolled with 2:1 randomization to remdesivir vs placebo
- Terminated early when pandemic was controlled
- Statistically underpowered

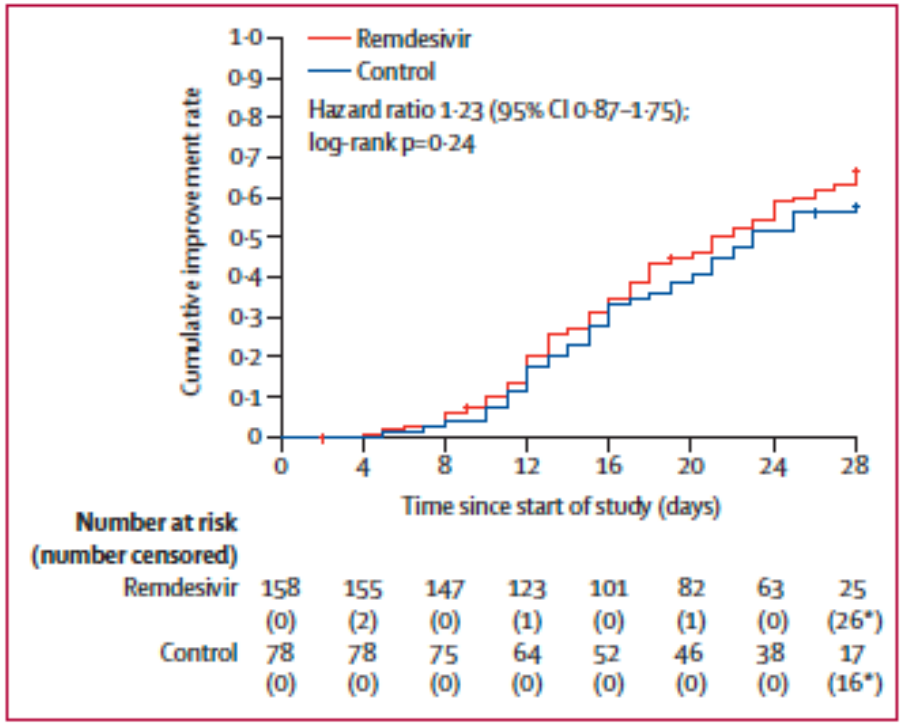
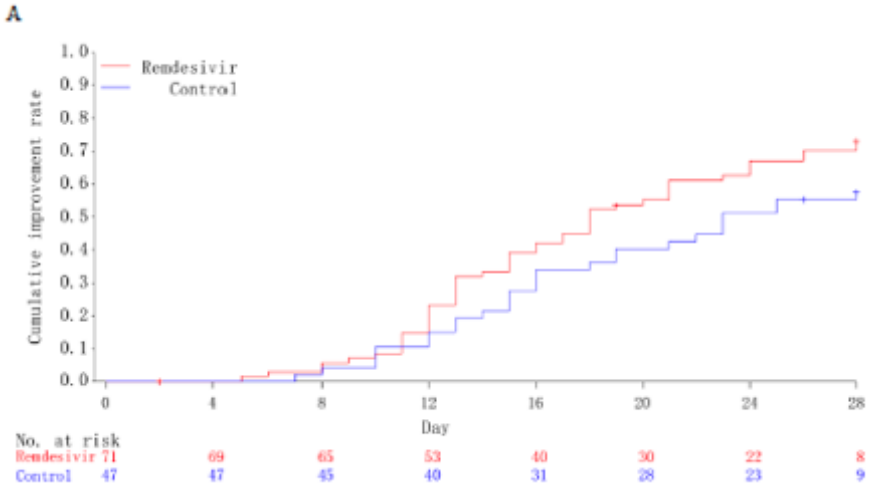


Figure 2: Time to clinical improvement in the intention-to-treat population

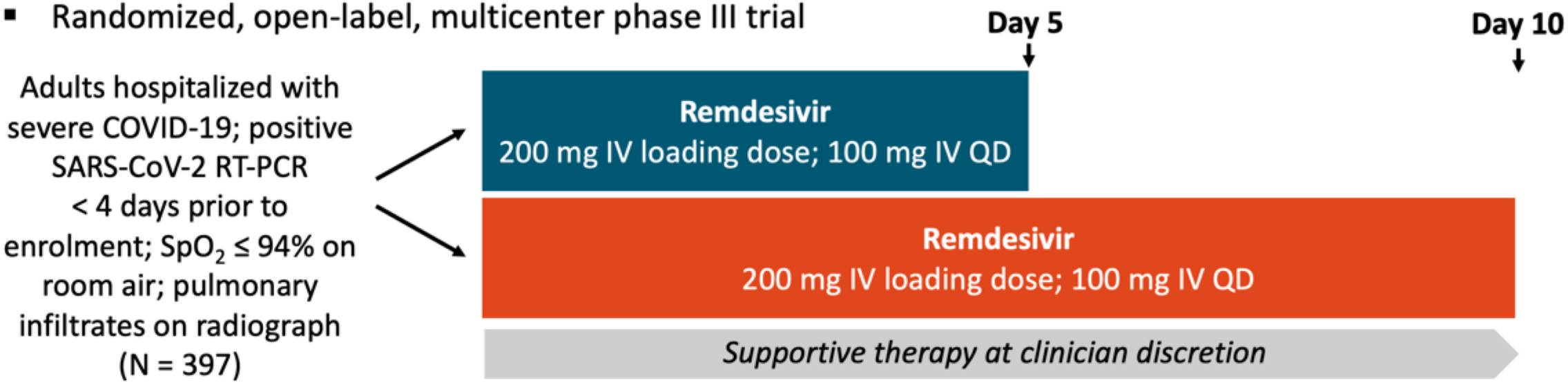
Median time to recovery for those with Symptoms ≤ 10 days was 18d for remdesivir vs 23d for placebo
HR 1.52; 95% CI 0.9 to 2.43



Wang Y, et al. Lancet 2020

GS-US-540-5773: Remdesivir for 5 vs 10 Days for Hospitalized Patients With Severe COVID-19

- Randomized, open-label, multicenter phase III trial



- Primary endpoint: time to clinical improvement (≥ 2-point improvement from BL on 7-point ordinal scale) at Day 14, time to all-cause mortality at Day 14
  - 10-day vs 5-day OR for clinical improvement at Day 14: 0.76 (95% CI: 0.51-1.13)[1]
- Current multivariate analysis* assessed risk factors for clinical improvement and all-cause mortality in combined population (5-day and 10-day dosing)[2]

*Competing risk analysis, where death is competing risk; RDV treatment duration and all risk factors as covariates.

1. Remdesivir EUA Provider Fact Sheet. 2. Marks. IAS COVID-19. Abstr 11803. Goldman JD, et al. NEJM 2020

- Clinical improvement of ≥ 2 points on the ordinal scale in 64% of participants in the 5d group vs 54% in the 10d group
- One day difference in time to clinical improvement and time to recovery
- Conclusion: Overall, no significant difference between the two groups

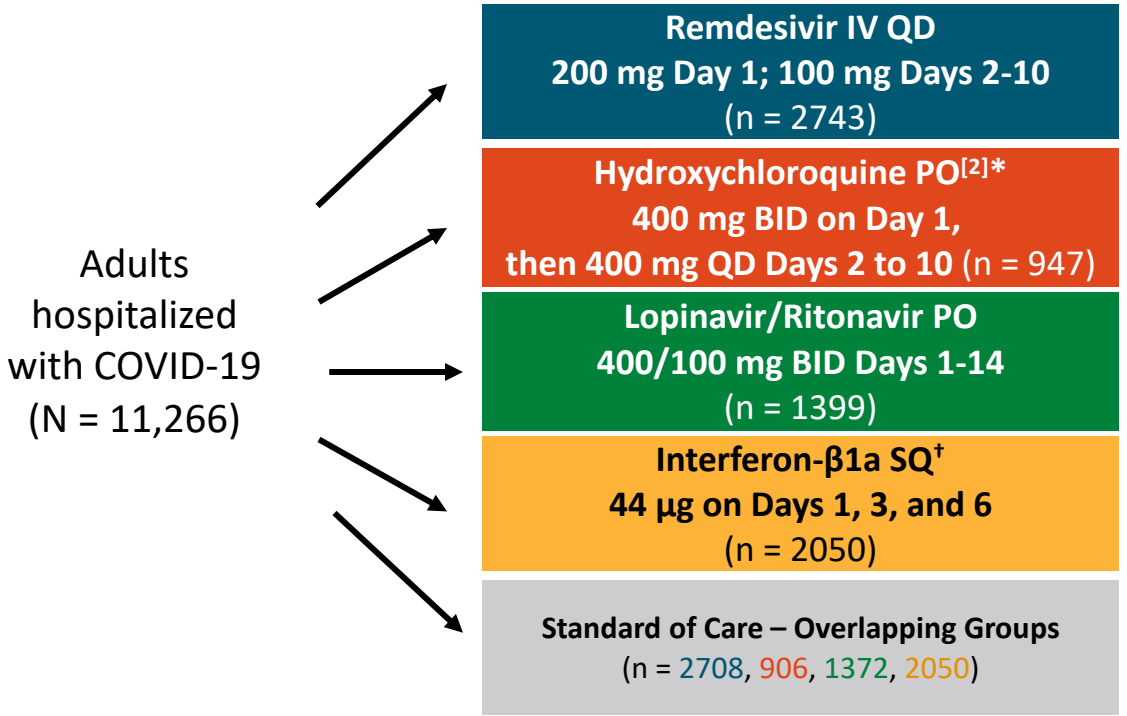
Goldman JD, et al. NEJM 2020

Table 2. Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7: Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (−7.0 to 7.5)
Day 7	71 (36)	54 (27)	−5.0% (−14.0 to 4.0)
Day 11	116 (58)	97 (49)	−4.8% (−14.1 to 4.6)
Day 14	129 (64)	107 (54)	−6.5% (−15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (−7.0 to 7.1)
Day 7	71 (36)	51 (26)	−6.0% (−14.8 to 2.7)
Day 11	115 (58)	97 (49)	−3.7% (−12.8 to 5.5)
Day 14	129 (64)	106 (54)	−6.3% (−15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	−2.3% (−10.5 to 5.9)
Day 7	84 (42)	69 (35)	−3.4% (−12.6 to 5.8)
Day 11	128 (64)	106 (54)	−5.7% (−14.6 to 3.2)
Day 14	140 (70)	116 (59)	−6.7% (−15.3 to 1.9)

WHO SOLIDARITY Trial: Antiviral Drugs to Treat Hospitalized Patients With COVID-19

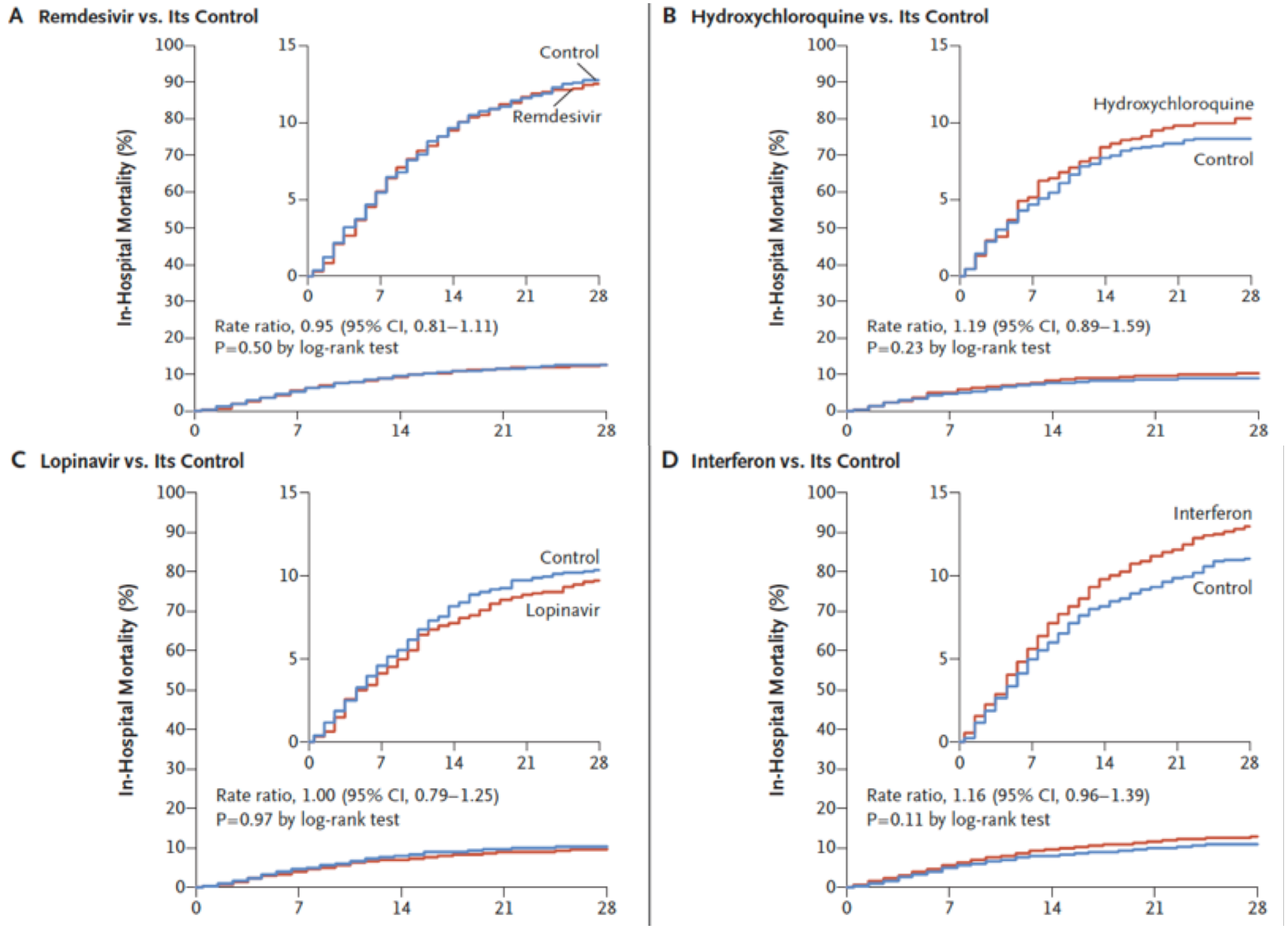
- Adaptive, open-label, randomized phase 3 trial conducted in 405 hospitals across 30 countries
- Primary endpoint: In-hospital mortality
- Secondary endpoints: Initiation of mechanical ventilation and duration of hospitalization



*Stopped on May 24, 2020; recommended dose from clinical trial study description.
†Given with LPV/RTV until July 4, 2020 (n = 651). Patients on high-flow oxygen, ventilators, or ECMO were given 10 µg IV daily for 6 days.

1. WHO Solidarity Trial Consortium. NEJM. 2020;[Epub]

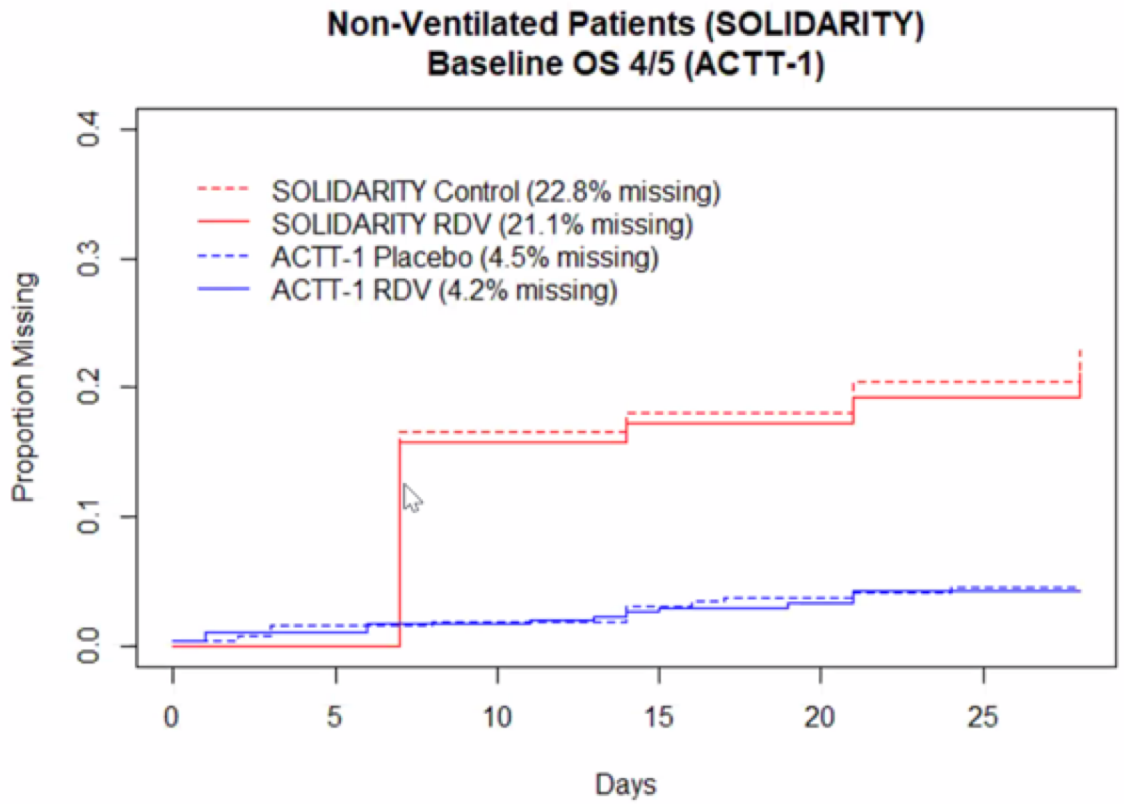
WHO SOLIDARITY: 28-Day Mortality

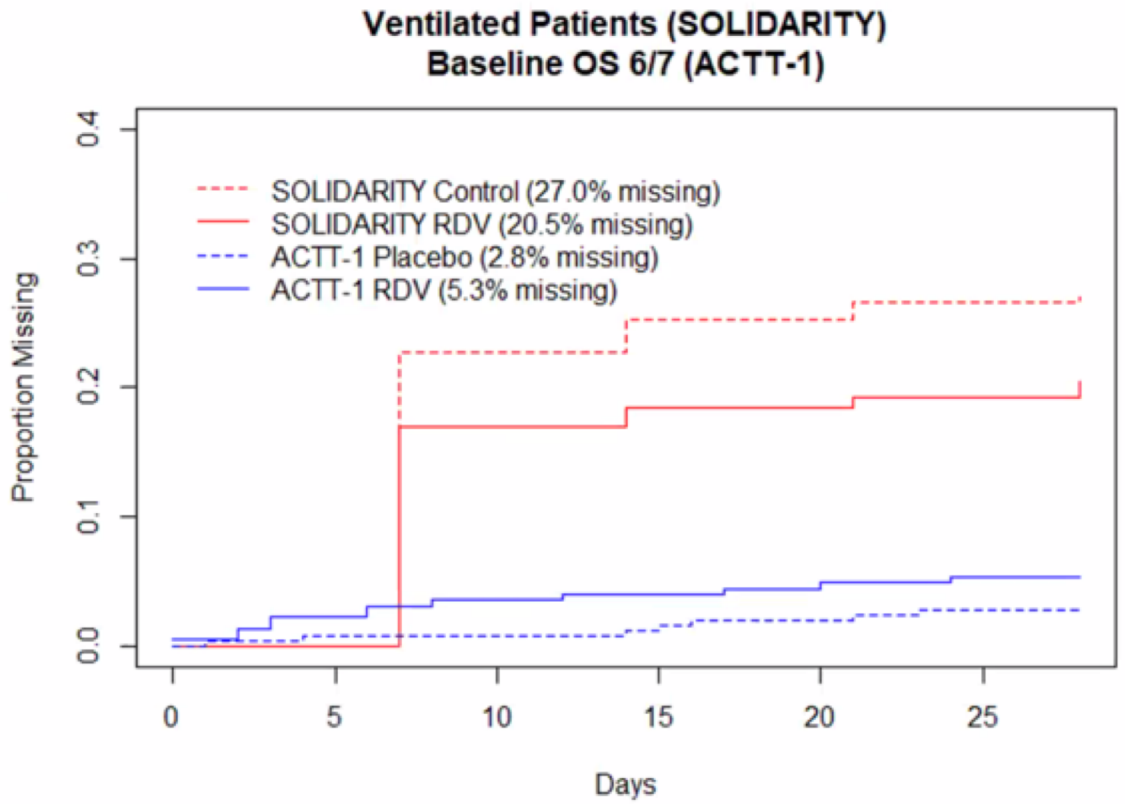


WHO SOLIDARITY: Summary & Limitations of Findings

- No study drug improved 28-day mortality overall, or when stratified by age, ventilation at entry, geographic region, or corticosteroid use
- Risk of bias was high in SOLIDARITY
  - Open-label design (no placebo control)
  - Choice of agents at randomization was dependent on drugs available at the site
  - Randomization was not stratified by site, background standard of care, disease severity at entry (other than mechanical ventilation) or symptom duration
  - SARS-CoV-2 diagnosis not confirmed in all patients
  - No monitoring or safety assessments
  - Supportive care was limited and highly heterogeneous (LMIC vs European)
  - Substantial missing data for the primary endpoint

Missing Data for the 28-Day Mortality Outcome
SOLIDARITY vs. ACTT-1





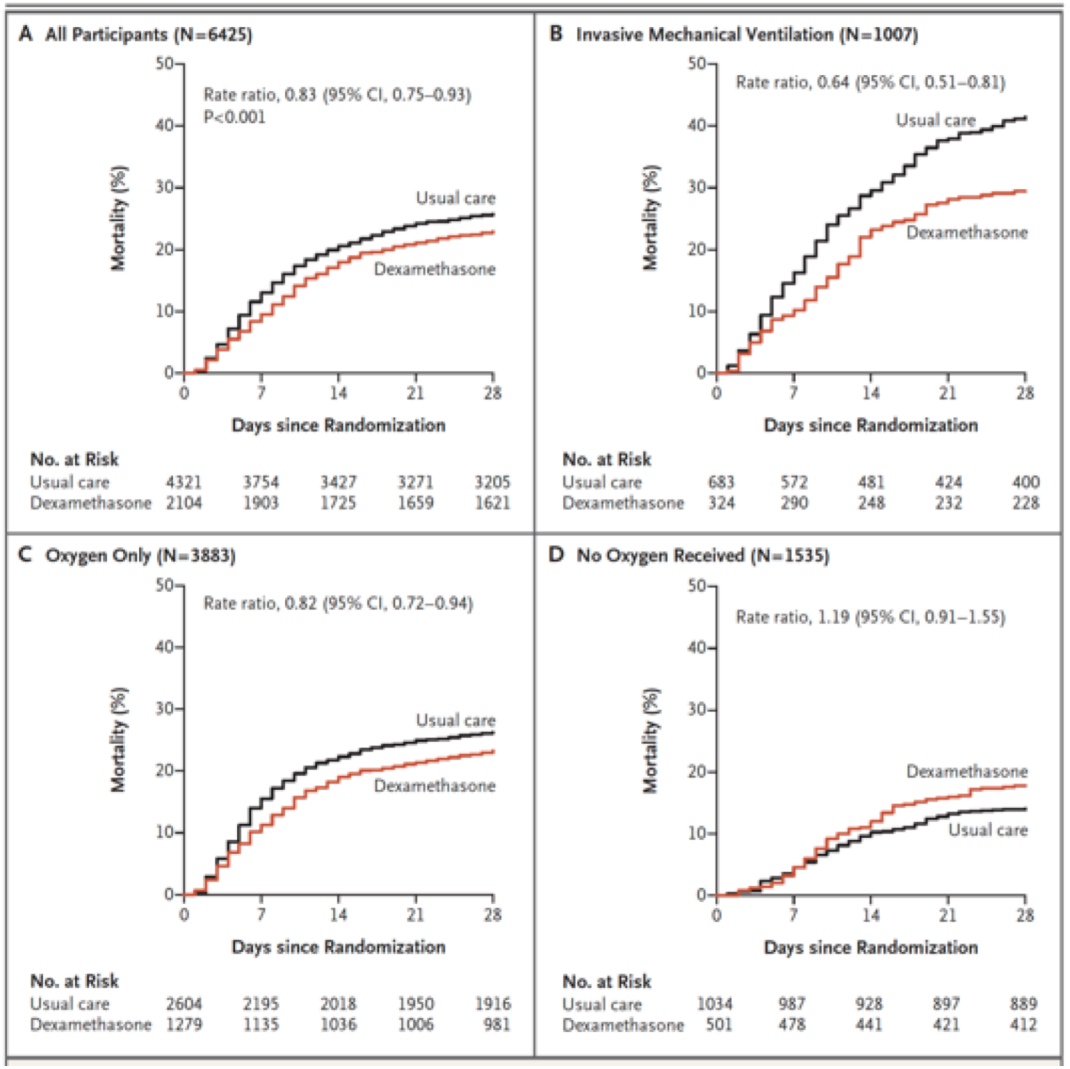
Anti-Inflammatory Therapy for Severe Covid-19: Dexamethasone & Baricitinib

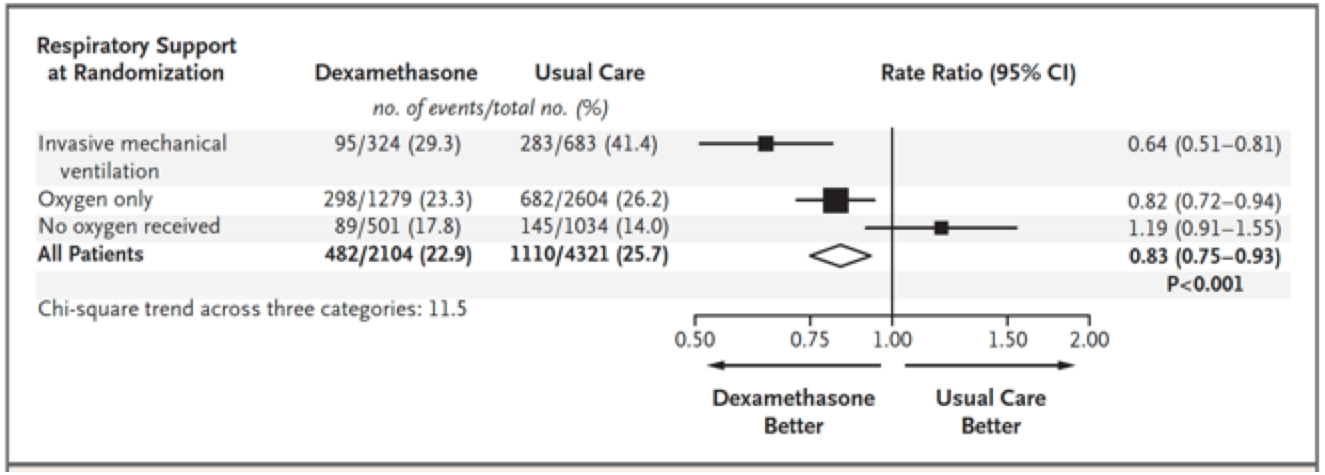
RECOVERY Trial: Dexamethasone vs Usual Care

- Study Design: Randomized, open-label, adaptive platform trial comparing different possible treatments with "usual care" in hospitalized pts with Covid-19 in 176 hospitals in UK
  - Clinically suspected or lab confirmed SARS-CoV-2 infection
  - Randomized 2:1 to usual care (N=4,321) or usual care + dexamethasone 6 mg/d for up to 10d (N=2,104) or to one of several treatments available at the site (HCQ, LPV-RTV, azithromycin, tocilizumab, convalescent plasma)
  - 1^0 endpoint 28d mortality; 2^0 outcomes → time to discharge, receipt and duration of mechanical ventilation, ECMO, cause-specific mortality, respiratory, renal, vital status at 28d

New Engl J Med July 2020; NEJM.org

RECOVERY: 28 Day Mortality





28d mortality:

- 22.9% in dexamethasone group vs. 25.7% in SOC (RR 0.83; 95% CI, 0.75-0.93; risk reduction 2.8%; P < 0.001)
- 29.3% vs. 41.4% (RR 0.64 [95% CI, 0.51- 0.81]; P < 0.001) for those on MV at entry
- 23.3% vs. 26.2% (RR 0.82; 95% CI, 0.72-0.94 for those on O_2 but not MV at entry
- Benefit primarily observed in pts with symptoms for more than 7d; **no benefit and possible harm in those hospitalized but not requiring O_2**

28-Day Mortality: Remdesivir ACTT-1 vs RECOVERY

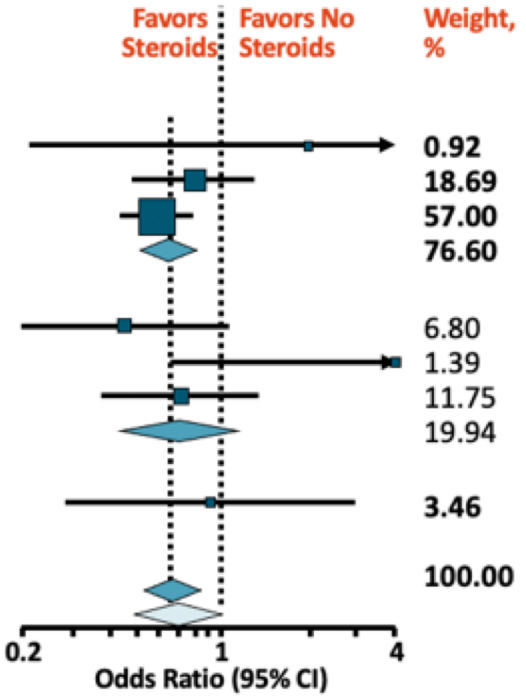
	ACTT-1 Remdesivir	ACTT-1 Placebo	RECOVERY Dex	RECOVERY SOC
No O_2 requirement (Ordinal score 4)	4.6%	5.6%	17.8%	14.0%
			Mortality Rate Ratio 1.19 (95% CI 0.91-1.55)	
O_2 requirement (Ordinal score 5)	4.3%	13.0%	23.3%	26.2%
High Flow O_2 (ordinal score 6)	23.3%	22.2%	Mortality Rate Ratio 0.82 (95% CI 0.72-0.94)	
MV or ECMO	22.7%	20.3%	29.3%	41.4%
			Mortality Rate Ratio 0.64 (95% CI 0.51-0.81)	
Overall	12.0%	15.2%	22.9%	25.7%
Overall Mortality Rate Ratio	0.79		0.83	

Limitations of RECOVERY Trial Results

- At entry, clinician could exclude arms/regimens if they felt the randomization was not appropriate for their patients
- Open-label; no placebo control
- Usual care is left up to the primary clinician and not standardized
- No interim data collection
- Those hospitalized but not on O_2 did worse on dexamethasone (no safety monitoring to determine reasons or attribution)
- Improved mortality with experience, expertise over time during the pandemic

Corticosteroids and 28-Day All-Cause Mortality in Critically Ill Patients With COVID-19

Drug/Trial	Initial Dose	Deaths/n		Odds Ratio (95% CI)	*P* Value
		Steroids	No Steroids		
Dexamethasone					
DEXA-COVID 19	High: 20 mg/day IV	2/7	2/12	2.00 (0.21-18.69)	
CoDEX	High: 20 mg/day IV	69/128	76/128	0.80 (0.49-1.31)	
RECOVERY	Low: 6 mg/day PO or IV	95/324	283/683	0.59 (0.44-0.78)	
Subgroup fixed effect		166/459	361/823	0.64 (0.50-0.82)	< .001
Hydrocortisone					
CAPE COVID	Low: 200 mg/day IV	11/75	20/73		
COVID STEROID	Low: 200 mg/day IV	6/15	2/14		
REMAP-COVID	Low: 50 mg every 6 hrs IV	26/105	29/92		
Subgroup fixed effect		43/195	51/179	0.69 (0.43-1.12)	.13
Methylprednisolone					
Steroids-SARI	High: 40 mg every 12 hrs IV	13/24	13/23	0.91 (0.29-2.87)	.87
Overall*					
Overall (fixed effects)		222/678	425/1025	0.66 (0.53-0.82)	< .001
Overall (random effects)		222/678	425/1025	0.70 (0.48-1.01)	.053

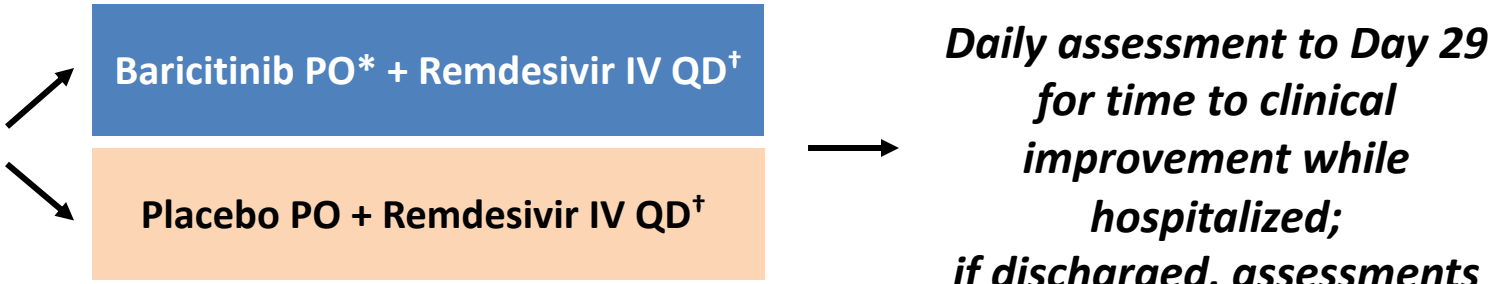


Combination Antiviral and Anti-Inflammatory Therapy

ACTT-2: Baricitinib + Remdesivir vs Remdesivir in Hospitalized Patients With Severe COVID-19

Multicenter, adaptive, randomized, double-blind, placebo-controlled phase 3 trial

Adult patients ≥ 18 yrs of age; hospitalized with confirmed SARS-CoV-2 infection and ≥ 1 of following: radiographic infiltrates by imaging; SpO_2 ≤ 94% on room air; requiring supplemental oxygen; or requiring mechanical ventilation
(**N = 1033**)



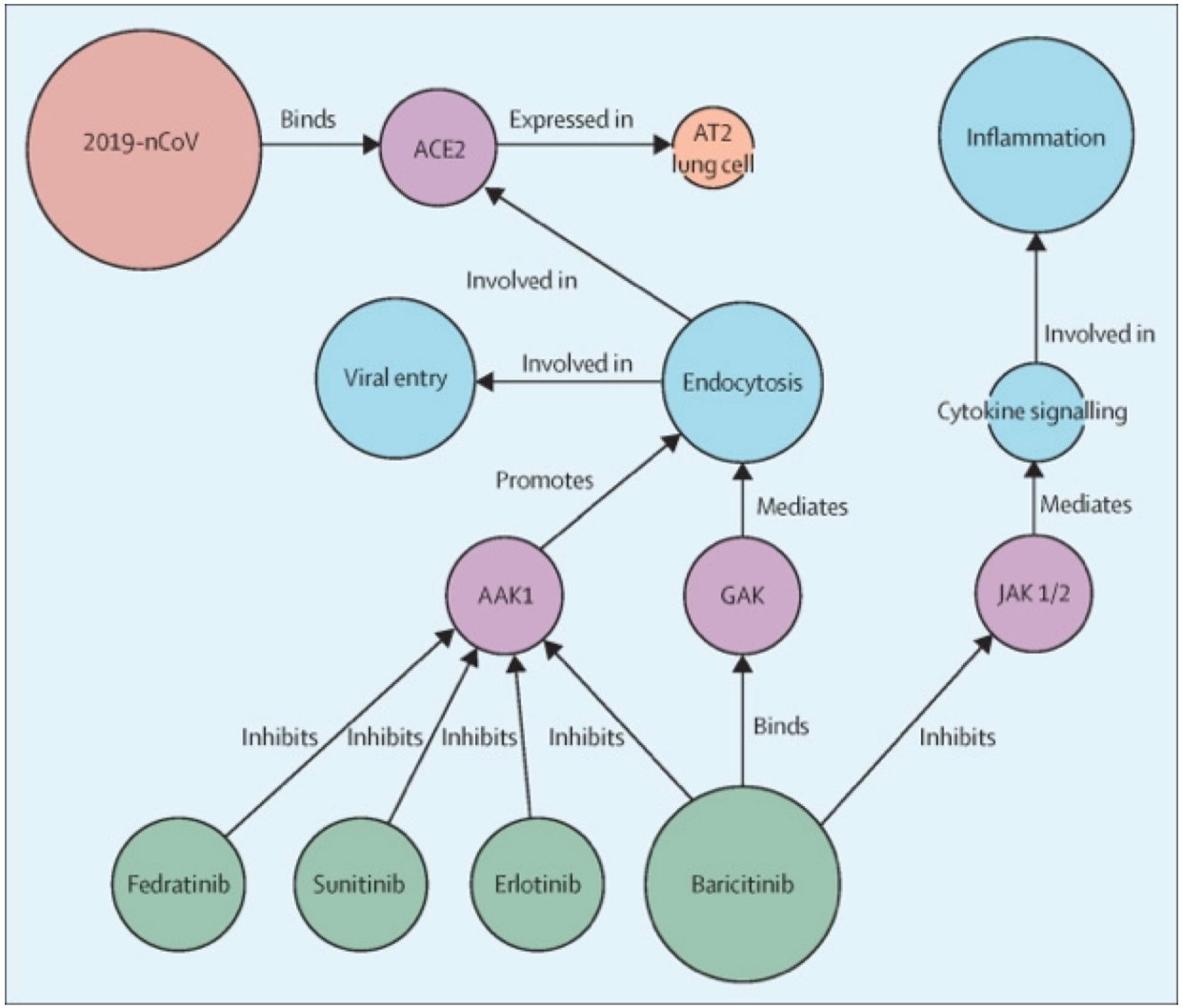
***4 mg** administered for duration of hospitalization, up to 14 days.
†200 mg on Day 1 followed by 100 mg on Days 2-10.

- Primary endpoint: time to recovery by Day 29 defined as the first day patient satisfies 1 of the top three ordinal scale categories same as for ACTT-1

1. NCT04401579. 2. Kalil AC, et al. NEJM 2021 at NEJM.org

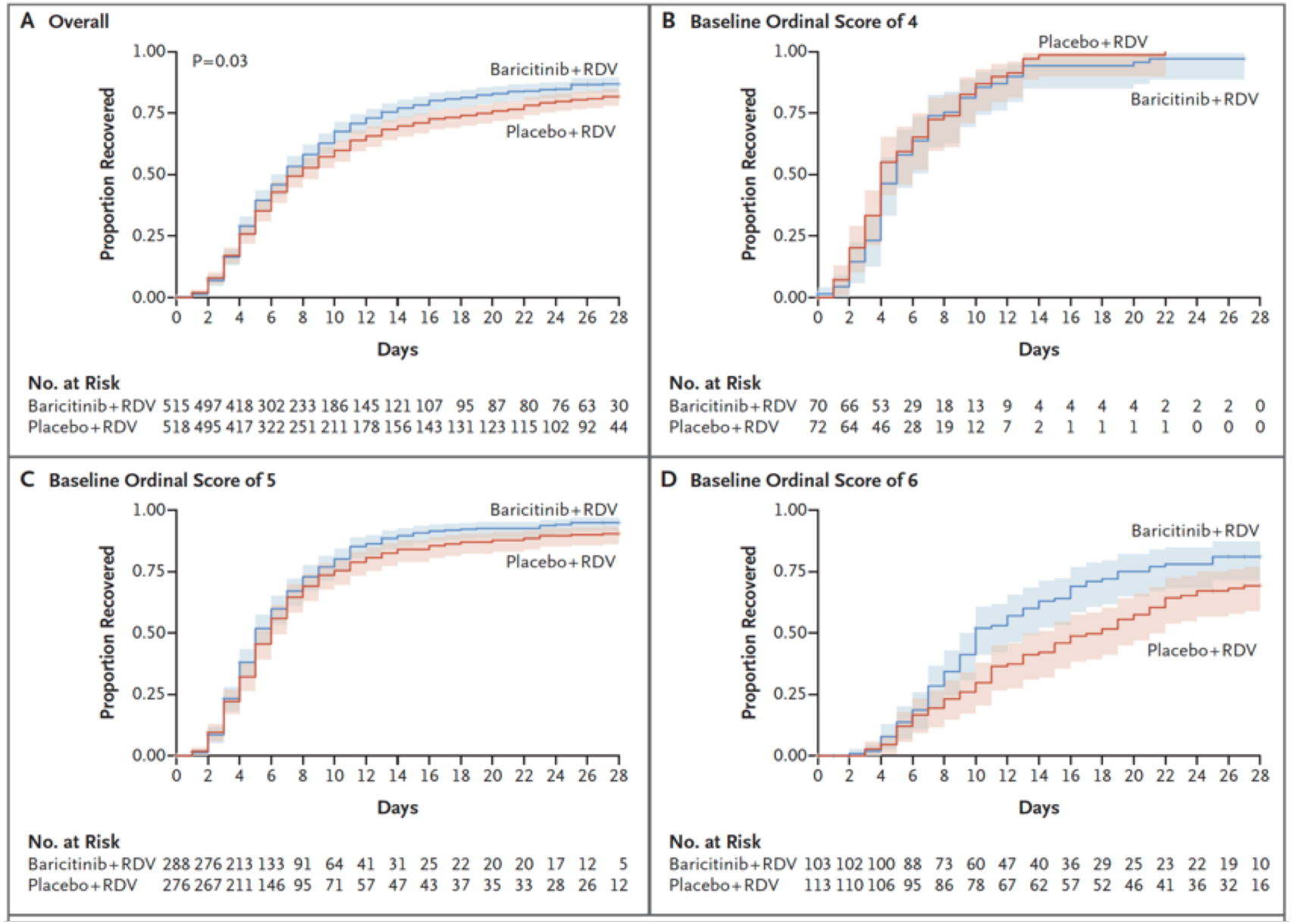
Why Baricitinib?

- JAK-1 and -2 inhibitor approved for treatment of rheumatoid arthritis (RA)
- Both anti-inflammatory and antiviral potential
  - Inhibits cytokine signaling and potentially viral entry at ACE2 receptor interface
- Risk of secondary infection due to immunosuppression and venous thrombosis in pts with RA and other autoimmune disorders

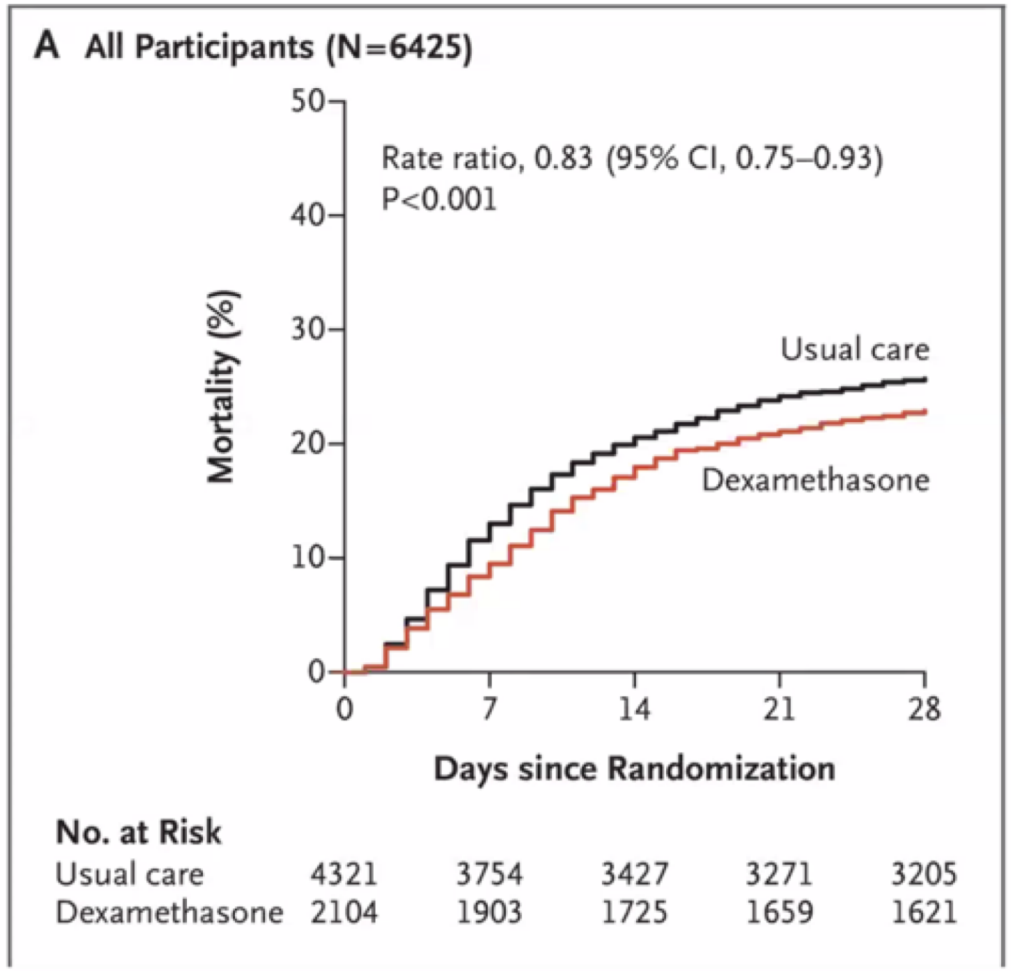


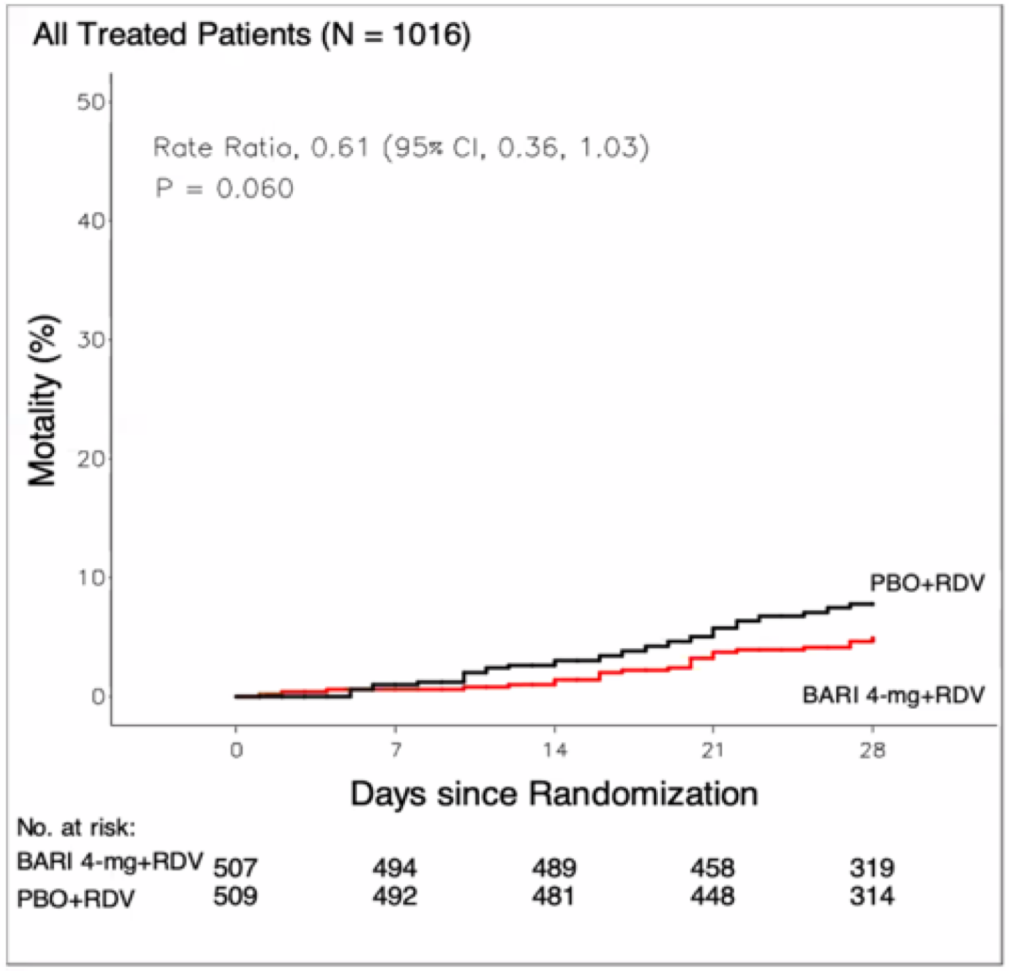
Richardson et al., Lancet 2020; 95:e30

ACTT-2 Results: Primary Outcome and by Baseline Ordinal Score



ACTT-2 vs. RECOVERY Trial Results





28-Day Mortality: Remdesivir ACTT-2 vs RECOVERY

	ACTT-2 Remdesivir	ACTT-2 Rem+Bari	RECOVERY Dex	RECOVERY SOC
No O_2 requirement (Ordinal score 4)	NE (0)	NE (0)	17.8%	14.0%
	Mortality HR NE		Mortality Rate Ratio 1.19 (95% CI 0.91-1.55)	
O_2 requirement (Ordinal score 5)	4.7%	1.9%	23.3%	26.2%
	Mortality HR 0.40 (95% CI 0.14-1.14)		Mortality Rate Ratio 0.82 (95% CI 0.72-0.94)	
High Flow O_2 (ordinal score 6)	12.9%	7.5%		
	Mortality HR 0.55 (95% CI 0.22-1.38)			
MV or ECMO (ordinal score 7)	22.6%	23.1%	29.3%	41.4%
	Mortality HR 1.0 (95% CI 0.22-2.22)		Mortality Rate Ratio 0.64 (95% CI 0.51-0.81)	
Overall	7.8%	5.1%	22.9%	25.7%
	Mortality Rate Ratio 0.65		Mortality Rate Ratio 0.83	

How do the differences between these trials influence interpretation?

- Higher risk of bias in the RECOVERY trial (confounding, selection bias, treatment response bias) due to inconsistencies in randomization, open-label, no placebo, choice of agents dependent on what was available at the site, randomization not stratified by site, disease severity or usual care
- Mortality rates different in control arms for both trials
  - Effect of a treatment in a population with a higher risk of death may not be the same in a population with a lower risk of death
- Critical difference in use of an active antiviral agent
  - Prevention of disease progression in ACTT-2 likely due to antiviral + anti-inflammatory effect; not evaluated in RECOVERY
- Safety profile for dexamethasone in this setting is unknown

What About Other Antiviral Drugs in Hospitalized Patients with Severe COVID-19?

- Randomized clinical trials showed no benefit of:
  - Hydroxychloroquine (with or without azithromycin)
  - Maraviroc and other HIV entry inhibitors
  - Lopinavir-ritonavir and other HIV protease inhibitors
  - Convalescent plasma
  - Monoclonal antibodies
- No adequately powered, placebo-controlled RCTs completed and observational studies with conflicting results for:
  - Ivermectin
  - Niclosamide
  - Favipiravir

Treatment of Severe COVID-19 Disease in Hospitalized Patients: Lessons Learned

- Remdesivir works
  - Reduces time to recovery, risk of further progression
  - Works better in combination with baricitinib
  - Improves survival in hospitalized patients in Ordinal Score 5 (low flow oxygen) ($SpO_2 \leq$ 94% on room air)
- Dexamethasone (or equivalent corticosteroid) works
  - Improves survival in hospitalized patients in Ordinal Score 6-7 (requiring high flow oxygen or mechanical ventilation)
  - We do not know whether dexamethasone and remdesivir are safe and effective when used in combination
  - We do not know if remdesivir + baricitinib is more effective that remdesivir + dexamethasone
- We need other safe, more effective antiviral and anti-inflammatory agents

Making Sense of Guidelines

“This pandemic is new and evolving; guidelines must evolve with it as our knowledge and clinical expertise improves.”

WHO Living Guidance: Corticosteroids for COVID-19*

Categories of Illness	Definition	Recommendation
Critical COVID-19	▪ ARDS, sepsis, septic shock ▪ Other conditions that would normally require life-sustaining therapies (mechanical ventilation) or vasopressor therapy	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Severe COVID-19	Any of the following: ▪ 0_2 < 90% on room air* ▪ RR > 30 breaths/min in adults and children aged > 5 yrs; RR ≥ 40 in children aged 1-5 yrs; RR ≥ 50 in children aged 2-11 mos ▪ Signs of respiratory distress (accessory muscle use, inability to complete full sentences; in children very severe chest wall indrawing, grunting, central cyanosis, etc)	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Non-severe COVID-19	▪ Absence of any signs of severe or critical COVID-19	▪ Suggest no corticosteroids

*Weak evidence to support use of remdesivir in any category of illness

NIH Guidelines: Therapeutic Management

Disease Severity	Recommendation
Not hospitalized, mild to moderate COVID-19	▪ ***Insufficient data*** to recommend for or against any specific antiviral or antibody ▪ **Bamlanivimab, casirivimab plus imdevimab *available through EUAs***, if high risk of disease progression ▪ ***Recommend against*** **dexamethasone**
Hospitalized but does not require supplemental oxygen	▪ ***Recommend against*** **dexamethasone** ▪ ***Insufficient data*** to recommend for or against **remdesivir**; may be appropriate if high risk of disease progression
Hospitalized and requires supplemental oxygen (but no high-flow oxygen, ventilation, or ECMO)	***Use 1 of the following:*** ▪ **Remdesivir** (eg, in case of minimal supplemental oxygen requirement) ▪ **Remdesivir** plus **dexamethasone** (eg, with increasing need for supplemental oxygen)* ▪ **Dexamethasone** (eg, if remdesivir cannot be used or is unavailable)
Hospitalized and requires high-flow oxygen or noninvasive ventilation	***Use 1 of the following:*** ▪ **Remdesivir** plus **dexamethasone*** ▪ **Dexamethasone**
Hospitalized and requires invasive mechanical ventilation or ECMO	▪ **Dexamethasone** ▪ ***For patients recently intubated,*** consider **remdesivir** plus **dexamethasone** (remdesivir alone not recommended)

*In rare case when corticosteroids cannot be used, **remdesivir** plus **baricitinib** available via EUA.

Remdesivir: 200 mg IV once, then 100 mg IV QD for 4 days or until discharge. Treatment may continue up to 10 days if no substantial clinical improvement by Day 5.
Dexamethasone: 6 mg IV or PO QD for 10 days or until discharge.
Baricitinib: 4 mg PO QD for 14 days or until discharge.

NIH COVID-19 Treatment Guidelines. Therapeutic management of patients with COVID-19. Last updated December 3, 2020.

UCSD Guidance For Treatment of Hospitalized Patients with COVID-19

Ordinal Scale (OS) / Disease Severity	Recommendations	Comments/Cautions	Ref
OS 4 (hospitalized, not requiring supplemental O_2)	Remdesivir alone (see guidance)	Dexamethasone should not be used.	NIH
OS 5 (hospitalized, requiring supplemental O_2, **FiO_2 < 15 L**)	**Refer to ACTT-4 Trial** If not eligible for ACTT-4, then: • RDV + dexamethasone *OR* • RDV + EUA baricitinib	Based on results from the ACTT-2 trial, strongly caution against RDV + dexamethasone AND baricitinib together* for COVID-19. *(Patients on steroids for non-COVID indications can be considered for baricitinib and continued steroids use with caution at provider discretion)* See EUA Baricitinib Guidance here See dexamethasone statement here	ACTT-2, RECOVERY
OS 6 (hospitalized, requiring NIV or **$FiO_2 \geq 15$ L**)*	**Refer to ACTT-4 Trial** If not eligible for ACTT-4, then: • RDV + dexamethasone *OR* • RDV + EUA baricitinib. If progresses to mechanical ventilation (OS 7), discontinue baricitinib		ACTT-2, RECOVERY
OS 7 (hospitalized, requiring MV or ECMO)**	RDV + dexamethasone Discontinue baricitinib	There are no data at this time to support the combined use of baricitinib and dexamethasone in this setting.	RECOVERY, NIH

Obrigado!

QUESTIONS?