Remdesivir (GS-5734)

A Review of Pertinent Drug Information for SARS-CoV-2

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Remdesivir (GS-5734)

Mechanisms:
1. Interference RNA-dependent RNA polymerase → delayed termination of RNA transcription 2. Template incorporation inhibiting complementary base addition/replication

Status: FDA Approved 10/22/2020

Formulation: Intravenous only, inhalational formulation in early trials

Dosing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

Manufacturer: Gilead Sciences

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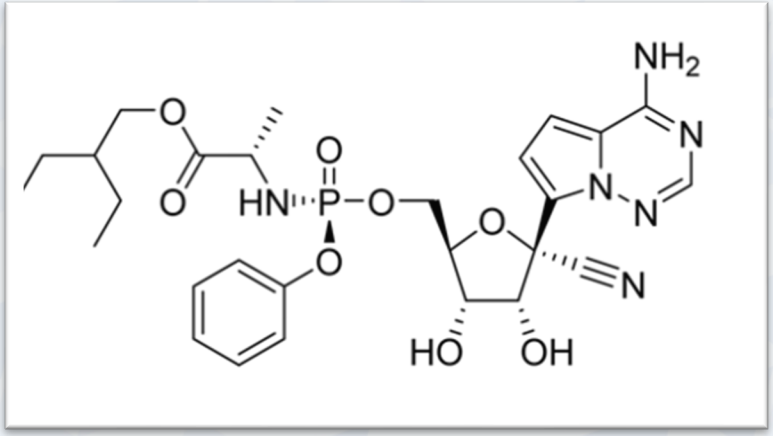
Tchesnokov; Viruses 2019. DOI: 10.3390/v11040326
Tchesnokov; J BiolChem 2020. DOI: 10.1074/jbc.AC120.015720

Remdesivir Structure Activity Relationship



Monophosphoramidate 1'Cyano C-adenosine Nucleoside Analog

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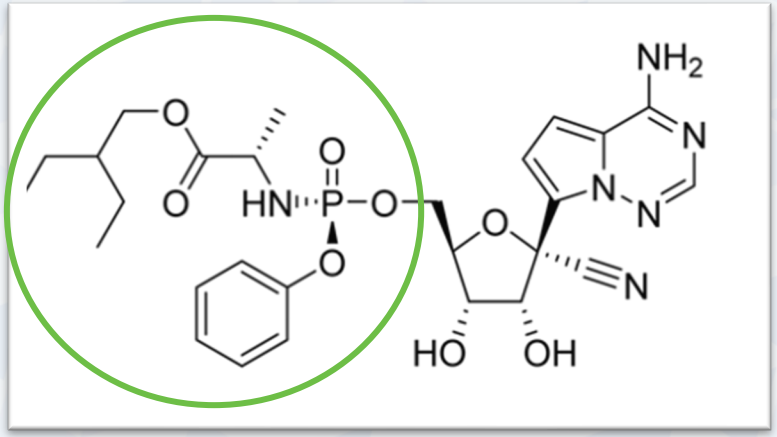
Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594

Remdesivir Structure Activity Relationship



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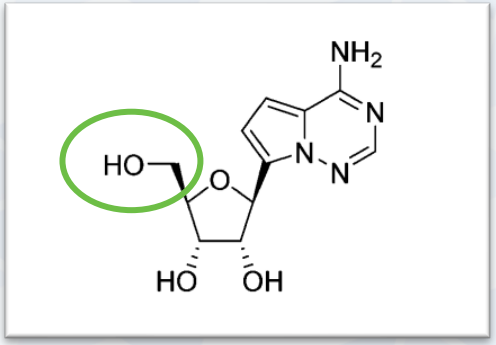
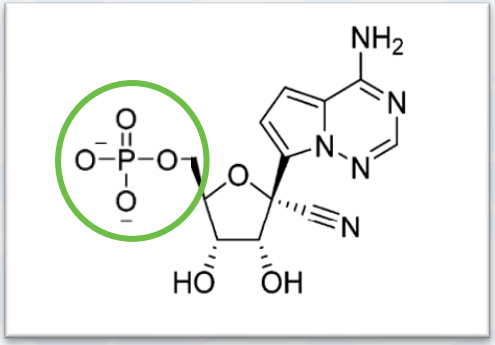


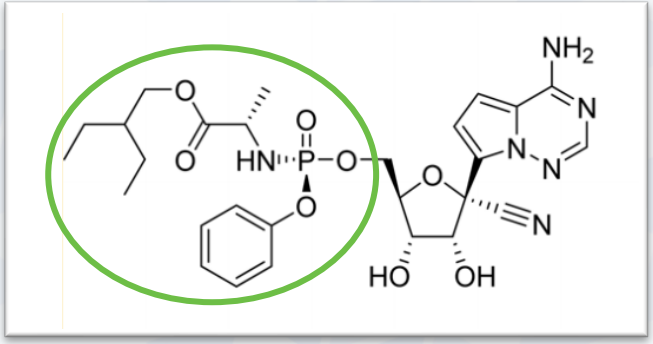
C-Adenosine Analog

Rate limiting phosphorylation



Monophosphate Form

Charge reduces permeability



Remdesivir

Neutral charge, bypasses rate limiting step

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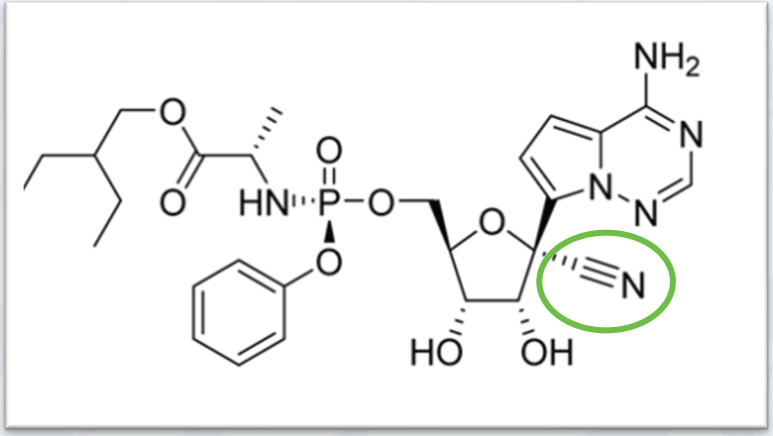
Remdesivir Structure Activity Relationship



Monophosphoramidate **1'Cyano** C-adenosine Nucleoside Analog

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Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594

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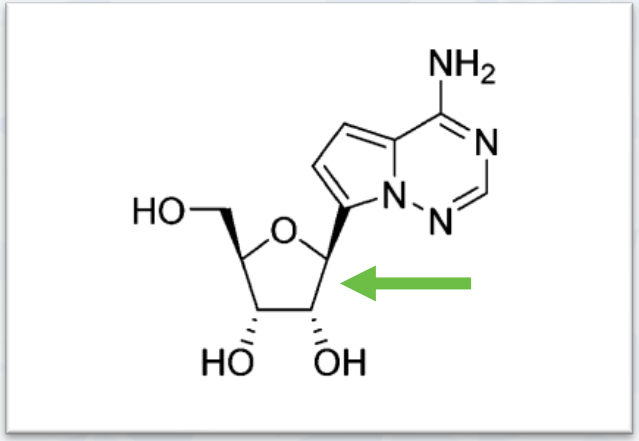
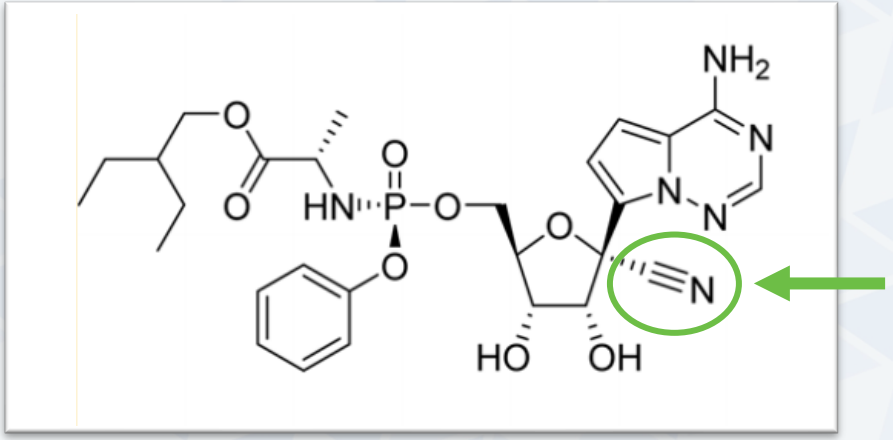


C-Adenosine Analog

Poor selectivity, highly cytotoxic



Remdesivir

1'Cyano modification confers selectivity

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Siegel; ACS 2017. DOI: 10.1021/acs.jmedchem.6b01594

Remdesivir (GS-5734) Pharmacokinetics

- **Distribution**: Unbound 12.1%; Widely distributed
  - Bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas
  - Seminal vesicle, epididymis, testes
  - Poorly crosses blood-brain barrier
- **Metabolism**: Phosphoramidate prodrug activated by esterases; CYP3A4 substrate
- **Elimination**: Predominantly in urine as GS-441524, partially in feces

Parameter	Remdesivir (GS-5734)	Nucleoside Metabolite (GS-441524)
C_{max}	2.6 µg/mL	0.14-0.15 µg/mL
T_{max}	-	1.5-2 hr
Half-life	0.89-0.98 hr	25.3 hr

Jorgensen; Pharm 2020. DOI: 10.1002/phar.2429

Safety

- Multiple-dose, 5-14 days
  - Any TEAE - 56-72%; All Grade 1-2
  - **ALT/AST increase**
    - Onset 5-25 days; resolution 3-47 days
  - Phlebitis
  - Extremity pain
  - Constipation
  - Dyspepsia
  - Nausea
  - Headache

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Sulfobutylether-beta Cyclodextrin (SBECD)

Remdesivir 100 mg solution - **6 g**
Remdesivir 100 mg lyophylized powder - **3 g**
Voriconazole 400 mg - **6.4 g**

Minimal clinical significance

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Adamsick; JASN 2020. DOI: 10.1681/ASN.2020050589

In vitro Activity

Filoviridae	*Paramyxoviridae*	*Pneumoviridae*	*Orthocoronaviridae*
• Ebola • Marburg	• Measles • Mumps • Nipah • Hendra	• Respiratory Syncytial Virus • Human Metapneumovirus	• HCoV-NL63 • HCoV-OC43 • HCoV-229E • HCoV-HKU1 • **MERS-CoV** • **SARS-CoV-1** • **SARS-CoV-2**

HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome;
SARS = Severe Acute Respiratory Syndrome

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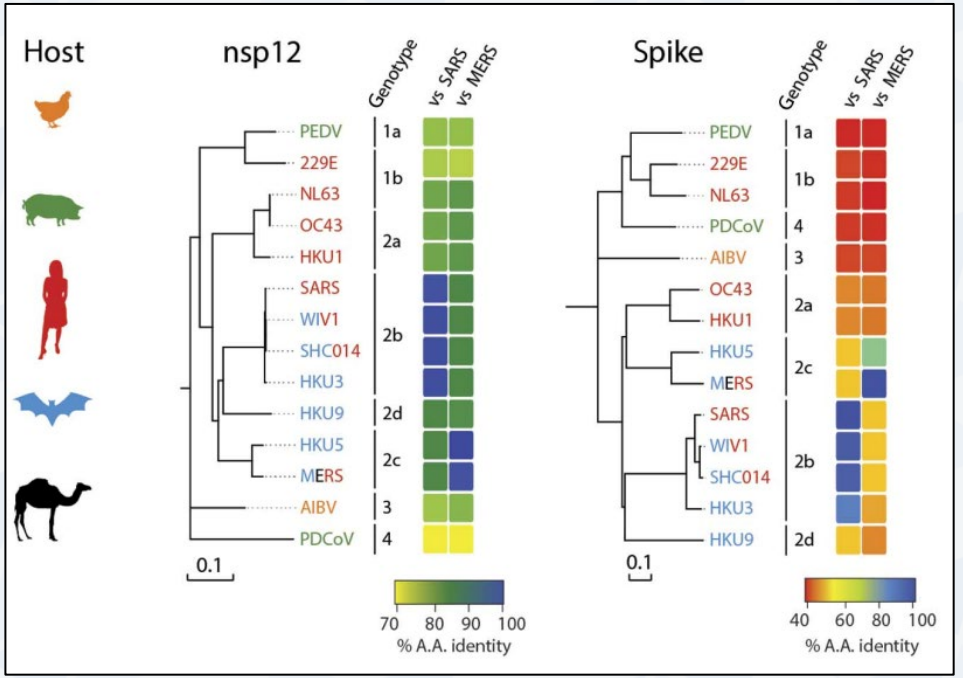
Brown; Antivir Res 2019. DOI: 10.1016/j.antiviral.2019.104541
Lo; Sci Rep 2017. DOI: 10.1038/srep43395
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653

In vitro Activity

Highly conserved nsp12 (RNA polymerase) across relevant coronaviruses

Broad activity against coronaviruses

Spike protein (viral cell entry) less conserved = host species diversity



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653

In vitro Activity

Virus	EC50 (cells)	CC50 (cells)	Selectivity Index
SARS-CoV-2	**0.01 µM (HAE)**	>100 µM (HAE)	>1000
SARS-CoV-1	0.069 µM (HAE)	> 10 µM (HAE)	>144
MERS	0.074 µM (HAE)	> 10 µM (HAE)	>135
Ebola	0.086 µM (MCr)	6.1 (Hep-2)	N/A

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells

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Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Gordon; J Bio Chem 2020. DOI: 10.1074/jbc.AC120.013056
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
Yao; *CID* 2020. DOI:10.1093/cid/ciaa237

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MERS		> 10 µM (HAE)	>135
Ebola	0.086 µM (MCF)	6.1 (Hep-2)	N/A

SARS-CoV-2 EC_{50}

Ribavirin 109.5 µM
Penciclovir 95.96 µM
Favipiravir 61.9 µM

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Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940
Gordon; J Bio Chem 2020. DOI: 10.1074/jbc.AC120.013056
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Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
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In vitro Activity

Analysis	Remdesivir			GS-441524	
Cell Line*	**Vero E6**	Calu3 2B4	**HAE**	Vero E6	Calu3 2B4
EC_{50} (µM)	**1.65**	0.28	**0.01**	0.47	0.62
24h RDV-TP (pmol/10^6 cells)	**0.54 ± 0.15**	2.17 ± 0.14	**10.6 ± 5.3**	2.37 ± 0.22	0.85 ±0.16

Cell lines: Vero E6 = African green monkey kidney cells; Calu3 2B4 = human lung cells; HAE = human airway epithelial cells; EC_{50} measured via plaque assay technique
RDV-TP = Remdesivir tri-phosphate (pharmacologically active)

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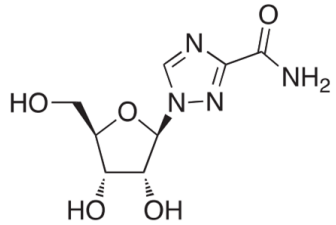
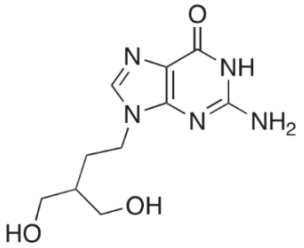
Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940

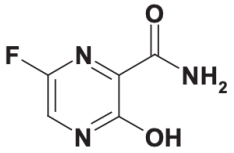
Coronaviruses and Proofreading



Ribavirin

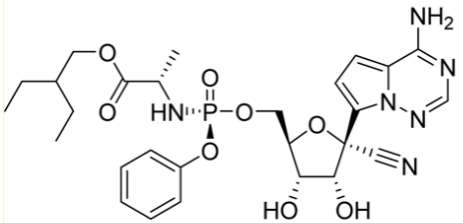


Penciclovir



Favipiravir

Removed by proofreading



Remdesivir

Maintains activity; high fitness cost

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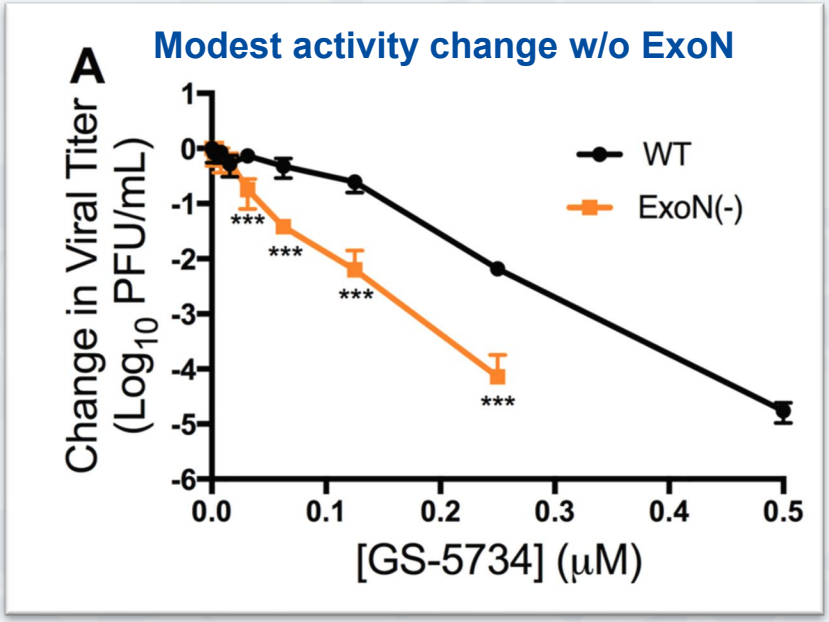
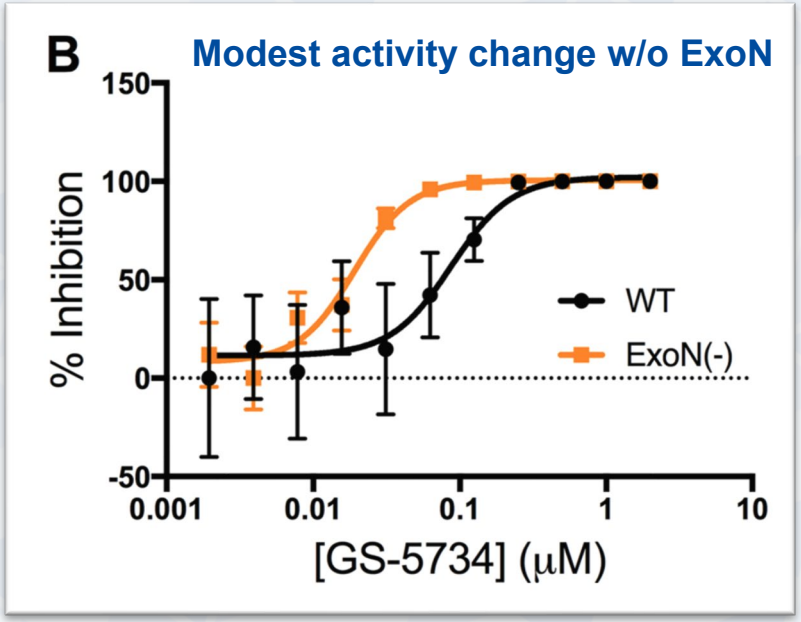
Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18
Smith; PLoS Pathog 2013. DOI: 10.1371/journal.ppat.1003565
Wang; Cell Res 2020. DOI: 10.1038/s41422-020-0282-0
Jordan; AAC 2018. DOI: 10.1177/2040206618764483.

Coronaviruses and Proofreading





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Agostini; Am Soc Micro 2018. DOI: 10.1128/mBio.00221-18

In vivo Animal Prophylaxis

Virus	Virologic	Clinical/Pathologic	Survival
SARS-CoV-1	✓	✓	✓
MERS	✓	✓	✓*

*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir

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De wit E; Proc Natl Acad Sci 2020. DOI: 10.1073/pnas.1922083117.
Sheahan; Nat Comm 2020. DOI: 10.1038/s41467-019-13940-6.
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653.

In vivo Animal Treatment

Virus	Virologic	Clinical/Pathologic	Survival
SARS-CoV-1	✓	✓	✓ (Day 1) ✗ (Day 2)
MERS	✓	✓	✗*
Ebola	✓	✓	---
SARS-CoV-2[&]	✓	✓	---

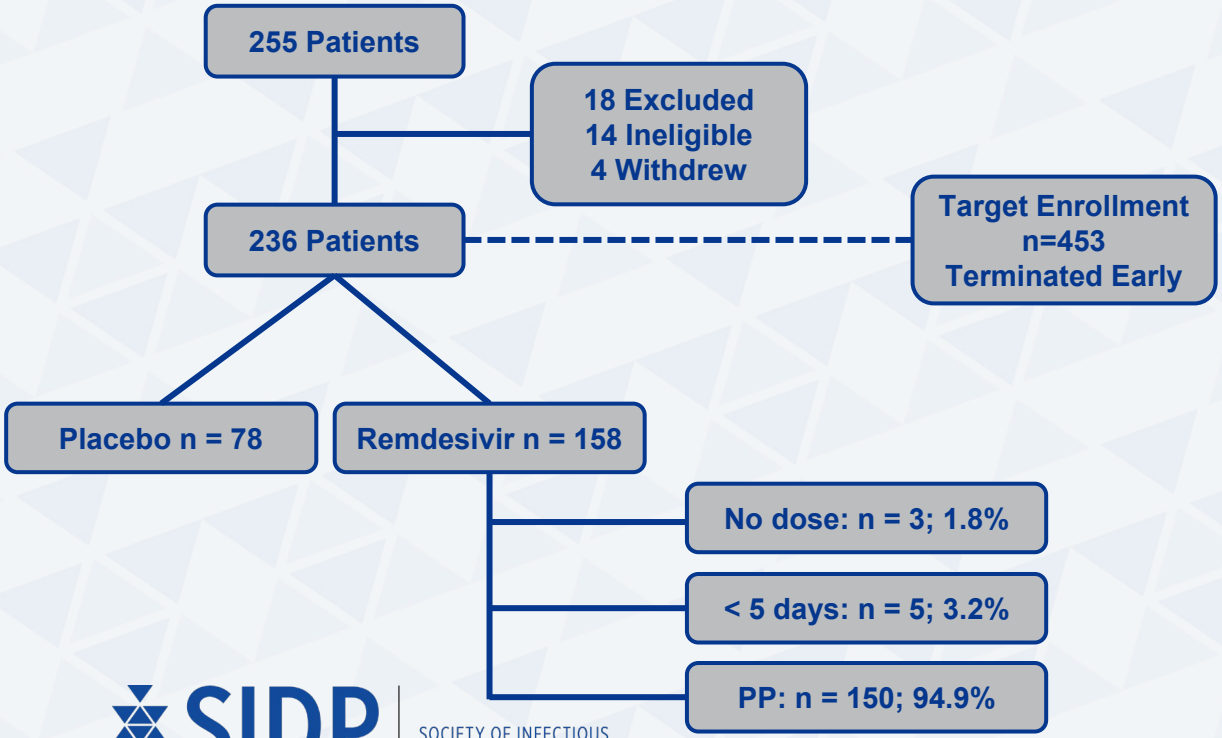
*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival

[&]Chimeric SARS-CoV strain expressing SARS-CoV2 RNA polymerase

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

De wit E; Proc Natl Acad Sci 2020. DOI: 10.1073/pnas.1922083117
Sheahan; Nat Comm 2020. DOI: 10.1038/s41467-019-13940-6
Sheahan; Sci Transl Med 2017. DOI: 10.1126/scitranslmed.aal3653
Warren; Nature 2016. DOI: 10.1038/nature17180
Pruijssers; Cell Reports 2020. DOI: 10.1016/j.celrep.2020.107940

Severe RCT in China



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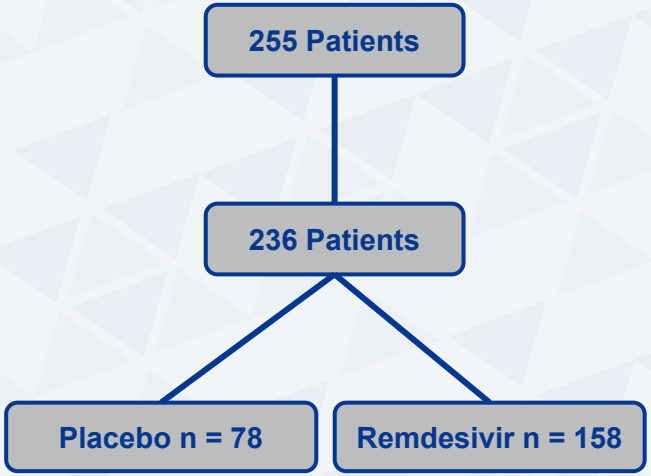
PP = Per protocol

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Severe RCT in China



Characteristic	Patients (n = 236)	
Median age (IQR) – yr	65 (56-71)	
Male sex – no. (%)	140 (59.3)	
Low-flow O_2 – no. (%)	**129 (82)**	**65 (83)**
HFNC/MV/ECMO – no. (%)	28 (18)	10 (13)
NEWS-2 – (IQR)	5 (3-7)	4 (3-6)
Median Sx (IQR) – days	10 (9-12)	
Coexisting conditions* – no. (%)	167 (70.7)	
Corticosteroids – no. (%)	91 (38.6)	

HFNC = high-flow nasal cannula; MV = mechanical ventilation; Sx = symptoms,
NEWS-2 = National Early Warning Score-2
*Most common = HTN (43.4%), diabetes (23.7%), coronary heart disease (7.2%)
Concomitant antivirals permitted – LPV/r (17.8%), IFN-a2b (18.7%)

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Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Severe RCT in China

Improvement = 2-pt Reduction

1. 1 - Discharged
2. 2 – Ambient air
3. 3 – Low-flow
4. 4 – High-flow/NIPPV
5. 5 – MV/ECMO
6. 6 – Death

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation

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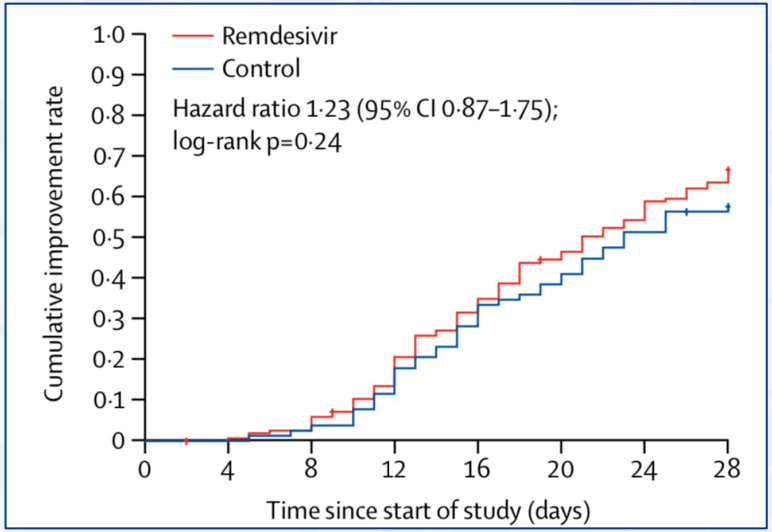
Time to Improvement

21 d (IQR 13-28) vs. 23 d (15-28)
HR 1.23 (95%CI 0.87-1.75)



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21 d (IQR 13-28) vs. 23 d (15-28)
HR 1.23 (95%CI 0.87-1.75)

Improvement – Early (<10 day)

18 d (IQR 12-28) vs. 23 d (15-28)
HR 1.52 (95%CI 0.95-2.43)

28-Day Mortality

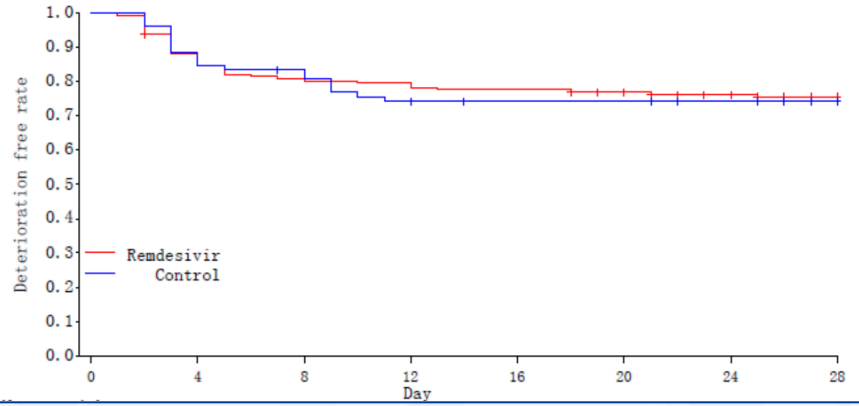
14% vs. 13%
Difference 1.1% (95%CI -8.1 to 10.3)

Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Severe RCT in China

Deterioration

Figure S4. Kaplan Meier of time-to-clinical deterioration (defined as one category increase or death) in the intention-to-treat population.



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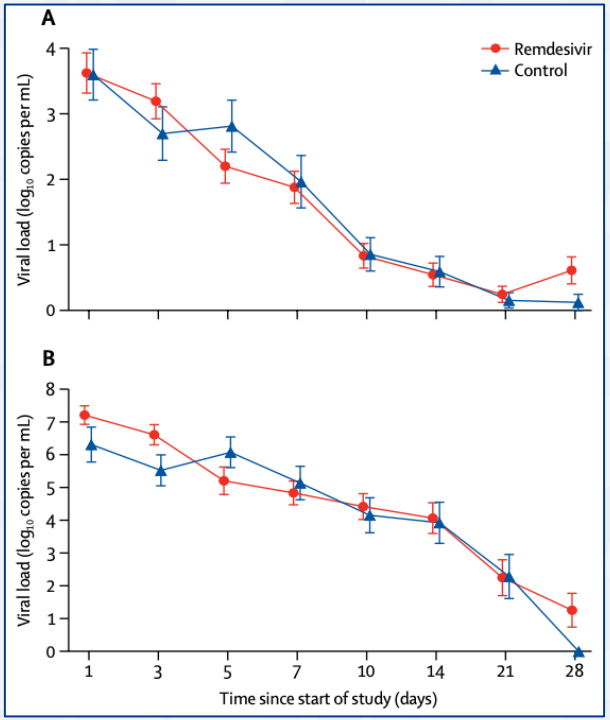
Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Viral Load



Severe RCT in China

Placebo-controlled data

"Our study found that remdesivir was adequately tolerated and **no new safety concerns were identified**."

Adverse Events	Remdesivir– n (%)	Placebo – n (%)
Any	102 (66)	50 (64)
AST elevation	7 (5)	9 (12)
Thrombocytopenia	16 (10)	5 (6)
Rash	11 (7)	2 (3)
Constipation	21 (14)	12 (15)
Serious	28 (18)	20 (26)
Acute Kidney Injury	1 (1)	0 (0)
Requiring Discontinue	18 (12)	4 (5)
ALT elevation	2 (1)	0 (0)
ARDS/resp. failure	7 (5)	1 (1)

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Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Severe RCT in China

Take home points:

- Placebo controlled, RCT
- Negative study
  - Underpowered – Remdesivir did not significantly reduce TTCR
  - Signal of larger reduction with early therapy (< 10-day) – interpret with caution
  - No difference in prevention of deterioration or mortality
- Safety
  - Well tolerated compared to control, low level of discontinuation

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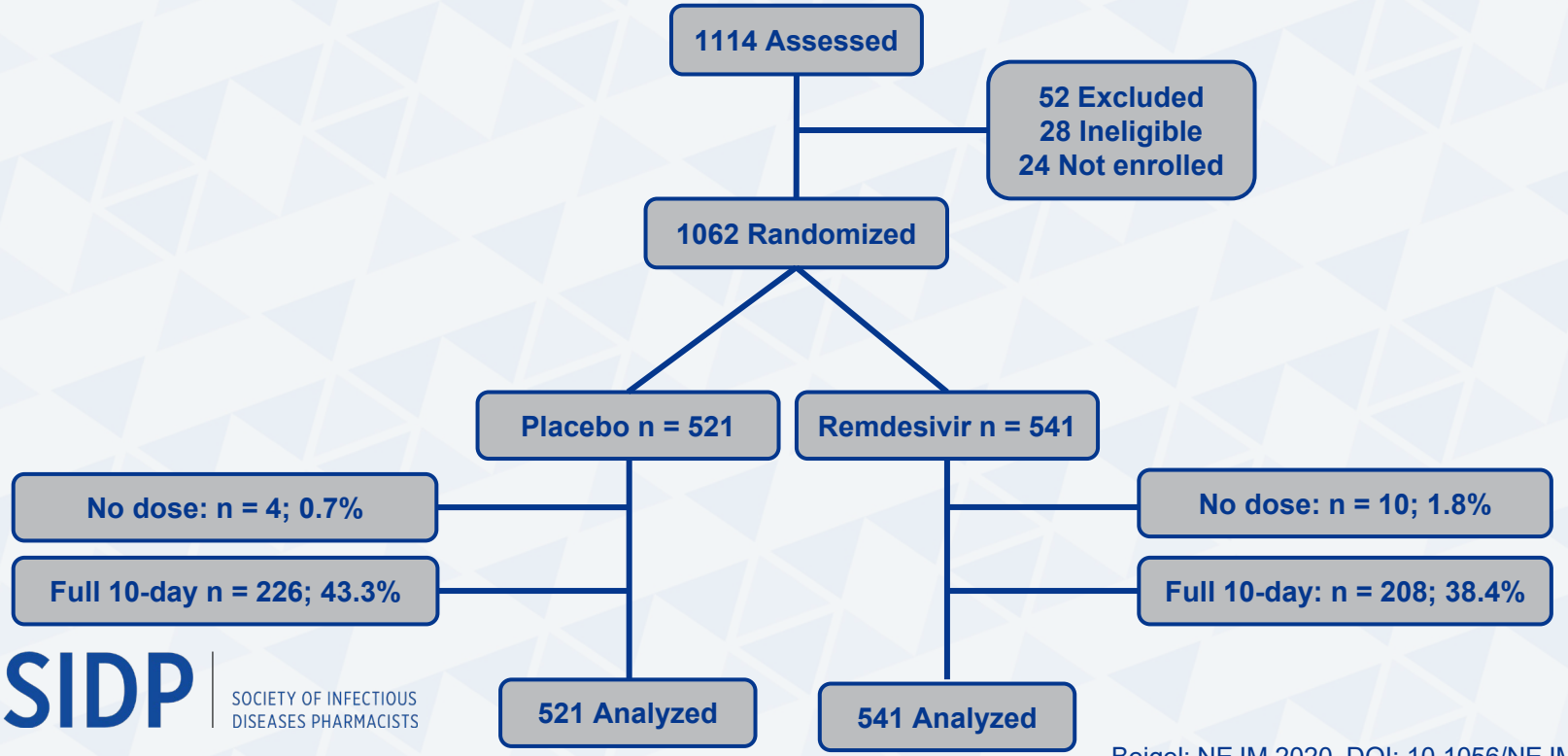
Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

Adaptive COVID Treatment Trial (ACTT-1)



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Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764

Adaptive COVID Treatment Trial (ACTT-1)

Characteristic	Remdesivir (n = 541)	Placebo (n = 522)
Mean age (SD) – yr	58.6 (14.6)	59.2 (15.4)
Male sex – no. (%)	352 (65.1)	332 (63.6)
Median Sx (IQR) – days	9 (6-12)	9 (7-13)
Comorbidities ≥ 2* – no. (%)	296 (55.7)	283 (54.7)
Baseline Status – no. (%)		
Baseline – 4 (Ambient Air)	75 (13.9)	63 (12.1)
Baseline – 5 (Low-flow)	**232 (42.9)**	**203 (39.0)**
Baseline – 6 (High-flow)	95 (17.6)	98 (18.8)
Baseline – 7 (MV/ECMO)	**131 (24.2)**	**154 (29.6)**

MV = mechanical ventilation; Sx = symptoms,
*Most common = HTN (50.6%), obesity (45.4%), diabetes (30.6%)

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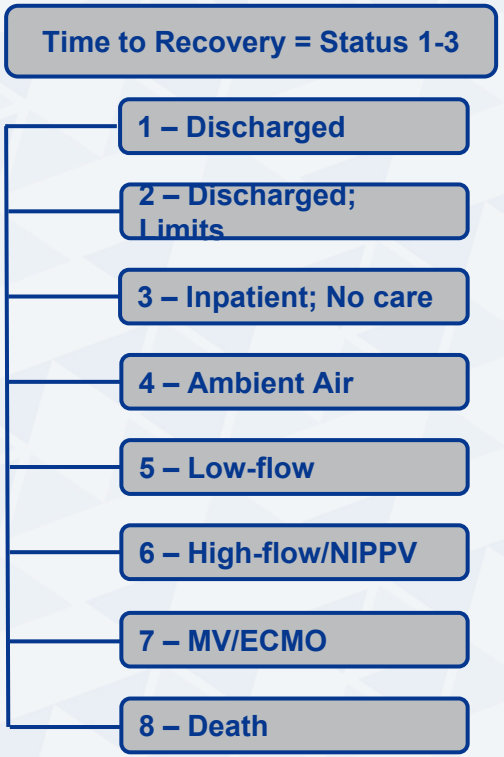


NIPPV = non-invasive positive pressure ventilation

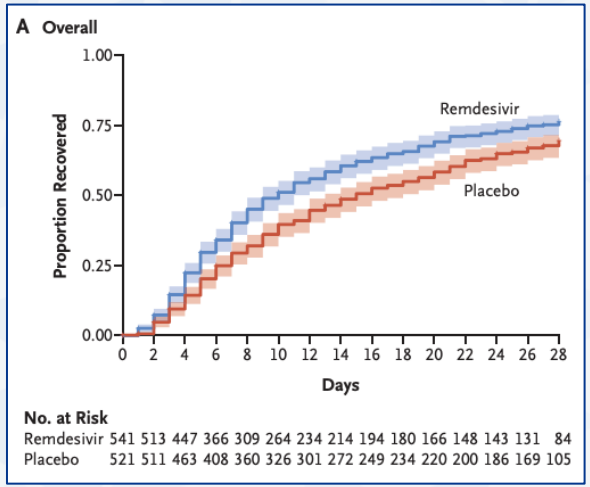
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery

Remdesivir 10 d vs. Placebo 15 d
RR 1.29 (95%CI 1.12-1.49; P<0.001)

Time to Recovery

Adjusted for baseline clinical status
RR 1.26 (95%CI 1.09-1.46)



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764

Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery

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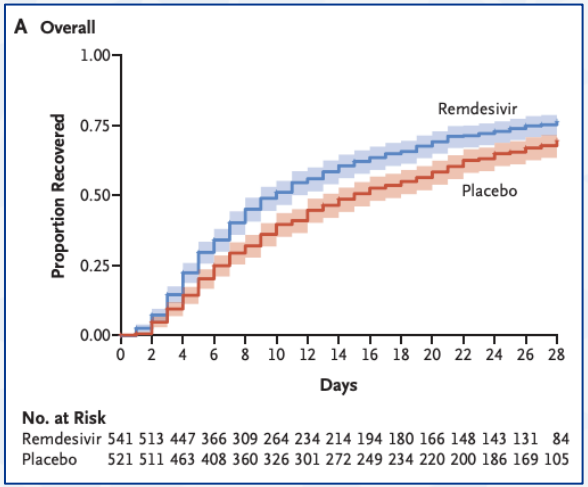

Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1062	1.29 (1.12–1.49)
Geographic region		
North America	847	1.30 (1.10–1.53)
Europe	163	1.30 (0.91–1.87)
Asia	52	1.36 (0.74–2.47)
Race		
White	566	1.29 (1.06–1.57)
Black	226	1.25 (0.91–1.72)
Asian	135	1.07 (0.73–1.58)
Other	135	1.68 (1.10–2.58)
Ethnic group		
Hispanic or Latino	250	1.28 (0.94–1.73)
Not Hispanic or Latino	755	1.31 (1.10–1.55)
Age		
18 to <40 yr	119	1.95 (1.28–2.97)
40 to <65 yr	559	1.19 (0.98–1.44)
≥65 yr	384	1.29 (1.00–1.67)
Sex		
Male	684	1.30 (1.09–1.56)
Female	278	1.31 (1.03–1.66)
Symptoms duration		
≤10 days	676	1.37 (1.14–1.64)
>10 days	383	1.20 (0.94–1.52)
Baseline ordinal score		
4 (not receiving oxygen)	138	1.29 (0.91–1.83)
5 (receiving oxygen)	435	1.45 (1.18–1.79)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	193	1.09 (0.76–1.57)
7 (receiving mechanical ventilation or ECMO)	285	0.98 (0.70–1.36)

0.33 0.50 1.00 2.00 3.00
Placebo Better | Remdesivir Better

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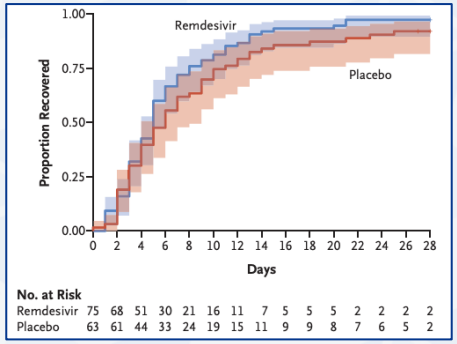
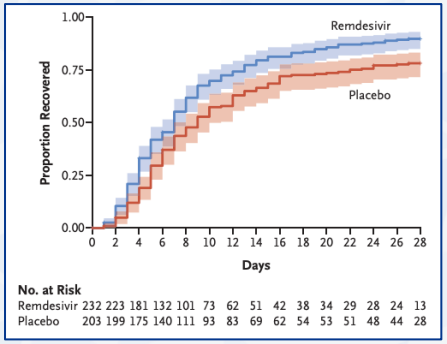
*Confidence intervals unadjusted for multiplicity; Should not be used to infer treatment effects

Adaptive COVID Treatment Trial (ACTT-1)

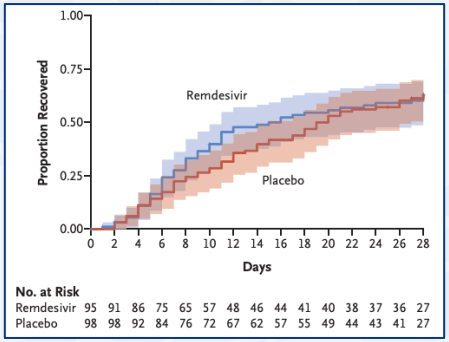
Ambient Air



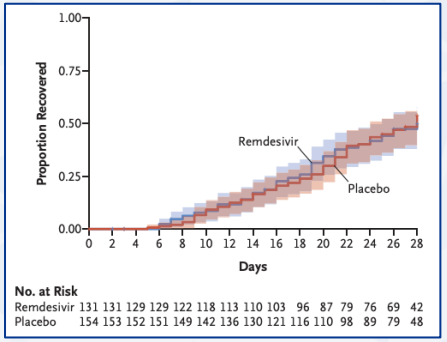
Low-flow



High-flow



MV/ECMO



"Interaction tests suggest greater benefit (with respect to recovery and mortality) in lower ordinal score categories"

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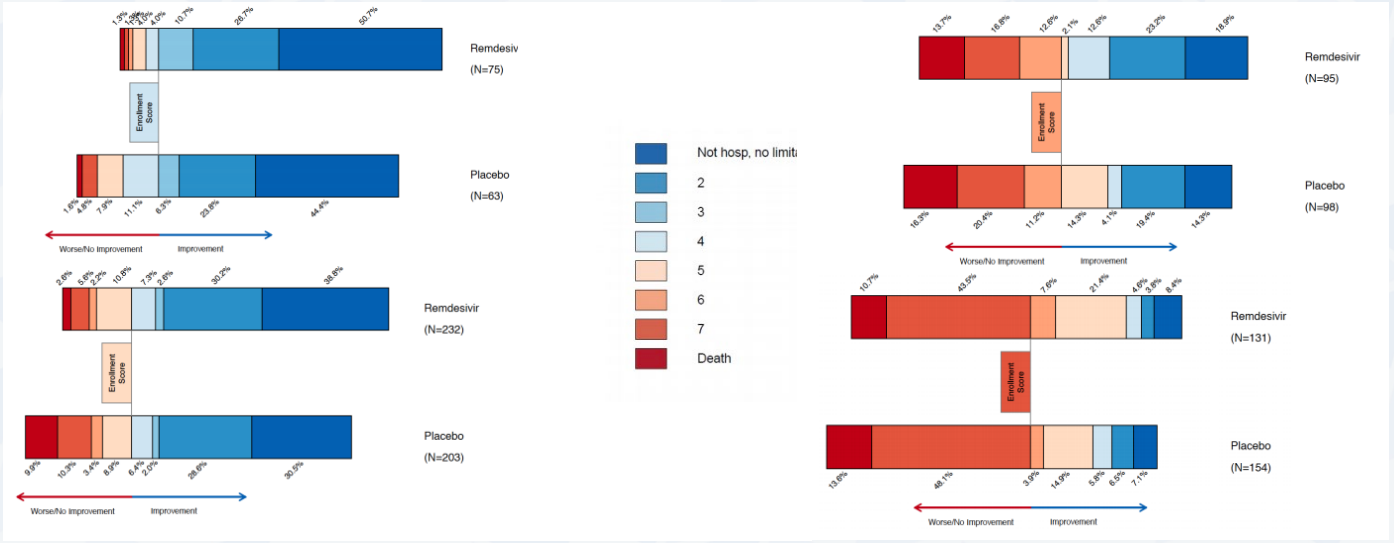
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 Clinical Worsening – Remdesivir vs. Placebo

Ambient Air
8.3% vs. 15.7%

Low-flow
10.4% vs. 23.6%



High-flow
30.5% vs. 36.7%

MV/ECMO
10.7% vs. 13.6%

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Adaptive COVID Treatment Trial (ACTT-1)

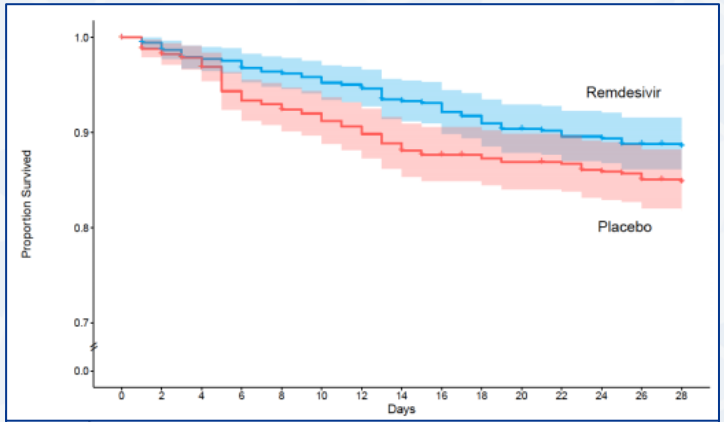
Mortality – Day 15

KM Estimate 6.7% vs. 11.9%
HR 0.55 (95%CI 0.36-0.83)

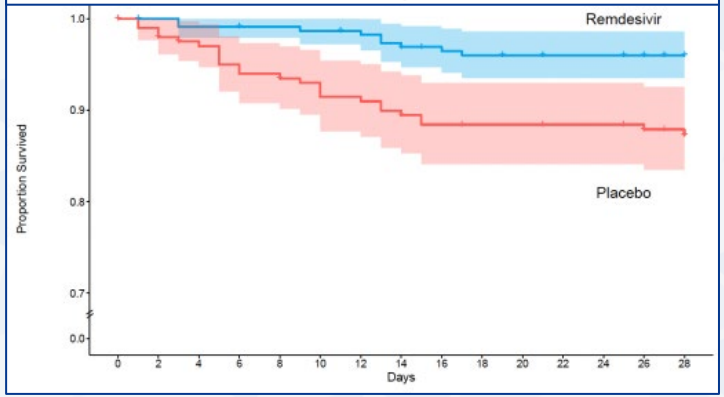
Mortality – Day 29

KM Estimate 11.4% vs. 15.2%
HR 0.73 (95%CI 0.52-1.03)

KM = Kaplan-Meier



All Patients



Low-flow

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Adaptive COVID Treatment Trial (ACTT-1)

Generally well tolerated overall

Higher rates of adverse events in placebo arm than remdesivir; High morbidity of disease

Adverse Events	Remdesivir (n = 541)	Placebo (n = 522)
Serious – n (%)	131 (25)	163 (32)
Acute kidney injury	9 (1.7)	17 (3.3)
Resp failure/distress	64 (12)	100 (19.4)
Hypotension/shock	9 (1.7)	11 (2.2)
Non-Serious	276 (51.9)	295 (57.2)
Anemia/Hgb decrease	42 (7.9)	52 (10.1)
Acute kidney injury	**55 (10.3)**	**74 (12.0)**
AST/ALT elevation	**30 (5.7)**	**57 (11.1)**
Lymphocyte decrease	44 (8.3)	54 (10.5)

Hgb = hemoglobin

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Adaptive COVID Treatment Trial (ACTT-1)

- **Largely consistent with preliminary report**
- Significant reduction in time to recovery
  - Similar benefit in baseline-adjusted analysis
  - Most prominently demonstrated in baseline category 5; largest group vs. most benefit?
  - No apparent benefit observed in MV/ECMO at baseline; follow-up time inadequate?
  - Benefit observed in subgroup ≤ 10 days, not > 10 days
    - Inconsistent trends by quartile, requires further confirmation
- Mortality
  - No statistically significant reduction in mortality
  - Baseline group 5 – lower mortality in remdesivir
- Safety
  - Lower adverse event rate compared to placebo group; well-tolerated

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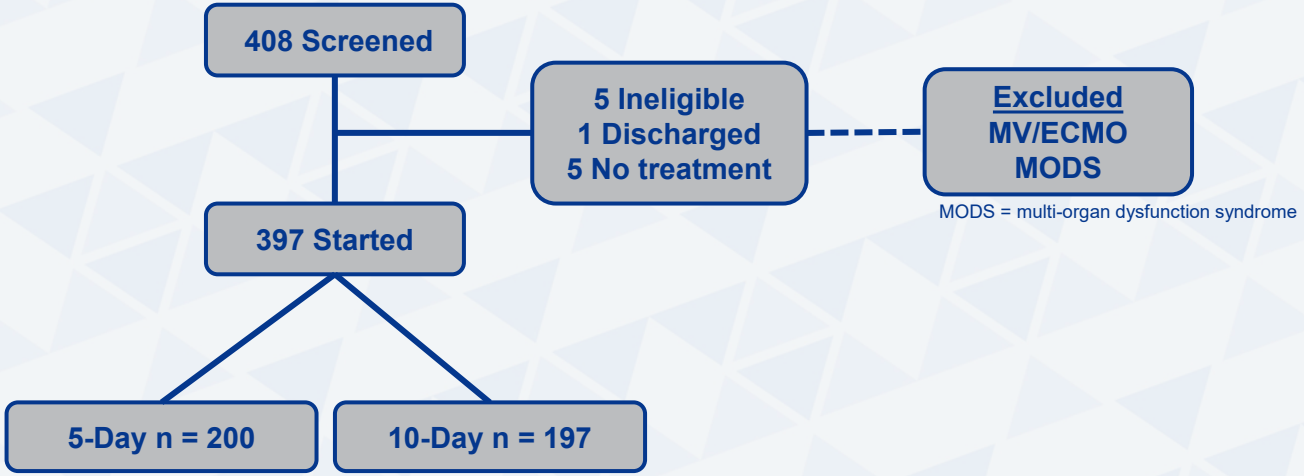
Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764

SIMPLE-1 Severe – 5 vs. 10 days



MODS = multi-organ dysfunction syndrome

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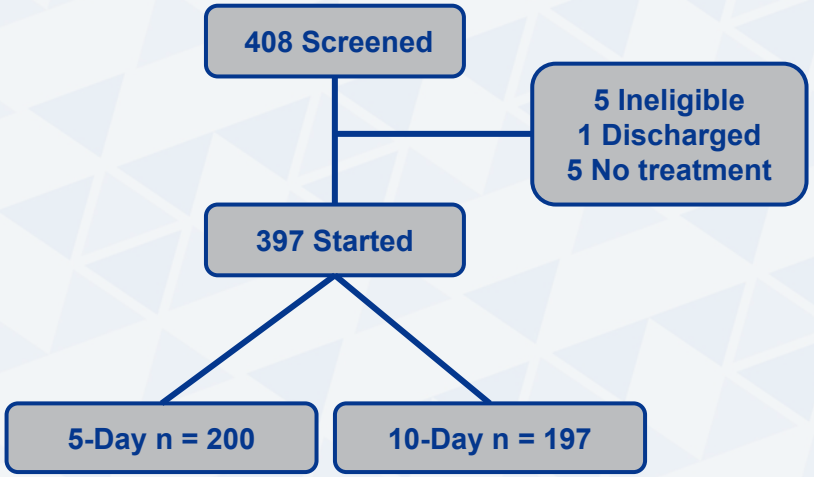
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days



Characteristic	5 Day (n = 200)	10 Day (n = 197)
Mean age (SD) – yr	58.6 (14.6)	59.2 (15.4)
Male sex – no. (%)	120 (60)	133 (68)
Median Sx (IQR) – days	8 (5-11)	9 (6-12)
Hosp. days before RDV (IQR)	2 (1-3)	2 (1-3)
Baseline Status – no. (%)[&]		
Baseline – Ambient Air	34 (17)	21 (11)
Baseline – Low-flow	113 (56)	107 (54)
Baseline – High-flow	49 (24)	60 (30)
Baseline – MV/ECMO	4 (2)	9 (5)

[&]P=0.02 for comparison via Wilcoxon rank-sum test

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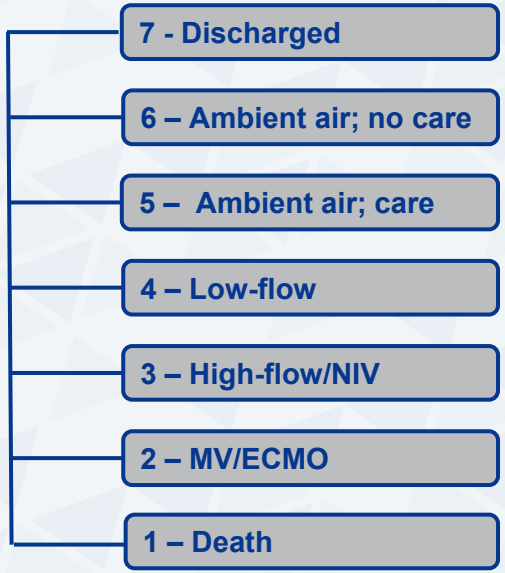
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days



MV = mechanical ventilation; NIV= non-invasive ventilation

14 Day Clinical Status

P=0.14
Stratified Wilcoxon rank-sum

Adjusted for baseline clinical status

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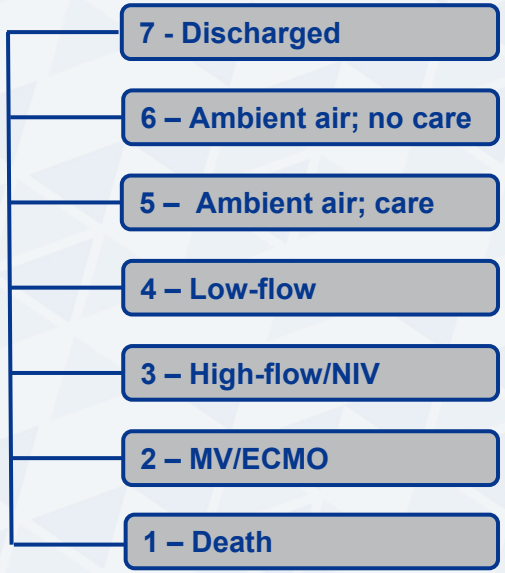
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days



MV = mechanical ventilation; NIV= non-invasive ventilation

14 Day Clinical Status

P=0.14
Stratified Wilcoxon rank-sum

Time to Improvement (2-pt)

10 d vs. 11 d
Adj. HR 0.79 (95%CI 0.61-1.01)

Time to Recovery (Score 6 or 7)

10 d vs. 11 d
Adj. HR 0.81 (95%CI 0.64-1.04)

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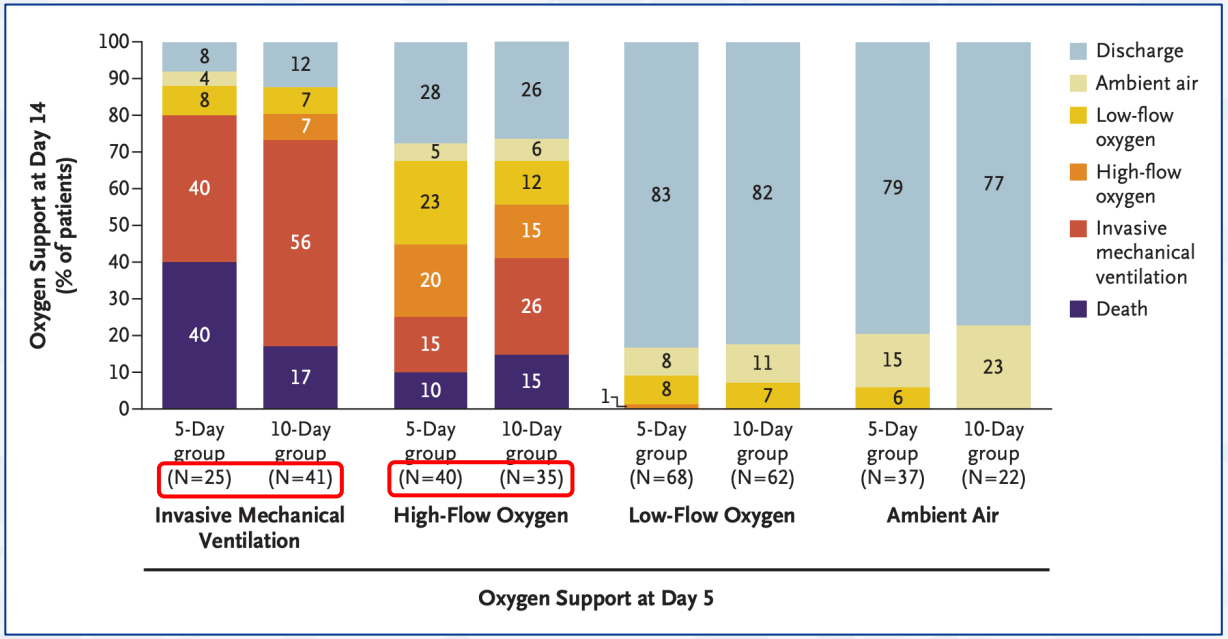
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days



Caution:

- Post-hoc analysis
- Small subgroups
- Inconsistent trends

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Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days

Day 14 Improvement

No. of Patients In Oxygen-Support Group at Day 14 (%)		5-day course of remdesivir (N=192)*				10-day course of remdesivir (N=188)*			
		Invasive (N=4)	Noninvasive (N=49)	Low-flow oxygen (N=107)	Ambient air (N=32)	Invasive (N=8)	Noninvasive (N=58)	Low-flow oxygen (N=102)	Ambient air (N=20)
		2	3	4	5/6	2	3	4	5/6
Death	1	1 (25)	8 (16)	5 (5)	2 (6)	4 (50)	13 (22)	2 (2)	2 (10)
Invasive	2	2 (50)	6 (12)	8 (7)	0	3 (38)	19 (33)	9 (9)	1 (5)
Non-invasive	3	0	7 (14)	2 (2)	0	0	4 (7)	3 (3)	1 (5)
Low-flow oxygen	4	1 (25)	7 (14)	8 (7)	2 (6)	0	5 (9)	6 (6)	0
Ambient air	5/6	0	2 (4)	11 (10)	0	0	2 (3)	8 (8)	3 (15)
Discharged	7	0	19 (39)	73 (68)	28 (88)	1 (12)	15 (26)	74 (73)	13 (65)
Improvement		**1 (25)**	**28 (57)**	**84 (79)**	**28 (88)**	**1 (12)**	**22 (38)**	**82 (80)**	**13 (65)**
Improvement: ACTT-1 Placebo		**44.3%**	**58.5%**	**74.5%**	**76.6%**	**44.3%**	**58.5%**	**74.5%**	**76.6%**

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Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-1 Severe – 5 vs. 10 days

Take home points:

- No significant difference between 5 vs. 10 days
  - Analysis adjusted for baseline clinical status
  - Important implications given limited supply
- MV/ECMO at day 5 receiving additional 5 days had lower mortality
  - Post-hoc analysis, small subgroups ≠ causal
  - Inconsistent trends (high-flow 10 day worse than 5 day)

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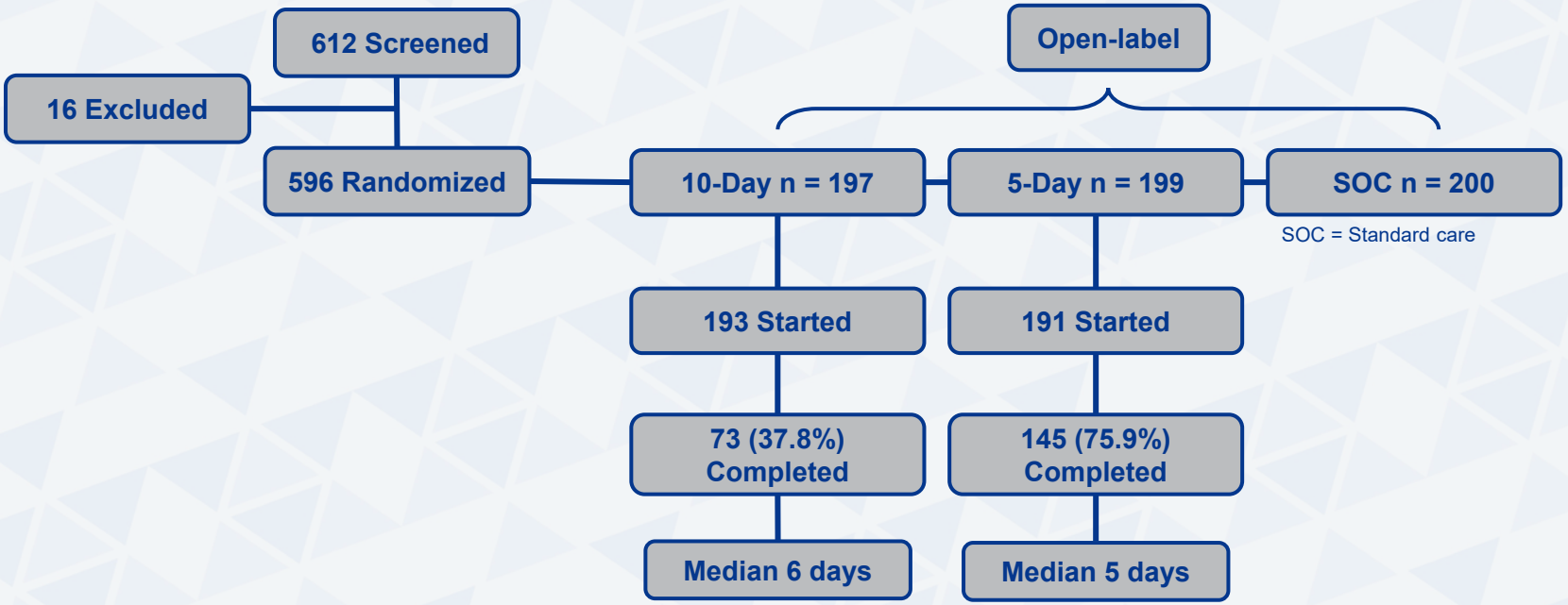
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Characteristic	10 Day (n = 197)	5 Day (n = 199)	SOC (n=200)
Median age (IQR) – yr	56 (45-66)	58 (48-66)	57 (45-66)
Male sex – no. (%)	112 (61)	114 (60)	125 (63)
Median Sx (IQR) – days	8 (5-11)	8 (5-11)	9 (6-11)
Hosp. days before RDV (IQR)	2 (1-3)	2 (1-3)	--
Baseline Status – no. (%)[&]			
Ambient air – No care	6 (3)	0	2 (1)
Ambient air – Medical care	**163 (84)**	**160 (84)**	**160 (80)**
Low-flow	23 (12)	29 (15)	36 (18)
High-flow	1 (1)	2 (1)	2 (1)
Steroids	29 (15)	33 (17)	38 (19)

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Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)

Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Characteristic	10 Day (n = 197)	5 Day (n = 199)	SOC (n=200)
Median age (IQR) – yr	56 (45-66)	58 (48-66)	57 (45-66)
Male sex – no. (%)	112 (61)	114 (60)	125 (63)
Median Sx (IQR) – days	8 (5-11)	8 (5-11)	9 (6-11)
Hosp. days before RDV (IQR)	2 (1-3)	2 (1-3)	--
Baseline Status – no. (%)[&]			
Ambient air – No care	6 (3)	0	2 (1)
Ambient air – Medical care	**163 (84)**	**160 (84)**	**160 (80)**
Low-flow	23 (12)	29 (15)	36 (18)
High-flow	1 (1)	2 (1)	2 (1)
Steroids	29 (15)	33 (17)	38 (19)

1º = Day 11 Clinical Status

- **7 – Discharged**
- **6 – Inpatient; No care**
- **5 – Inpatient; Care**
- **4 – Low-flow**
- **3– High-flow**
- **2 – MV/ECMO**
- **1 – Death**

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)

Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

1º = Day 11 Clinical Status

- 7 – Discharged
- 6 – Inpatient; No care
- 5 – Inpatient; Care
- 4 – Low-flow
- 3 – High-flow
- 2 – MV/ECMO
- 1 – Death

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Day 11 – Clinical Status

5-day vs. SOC: OR 1.65 (1.09-2.48); *P* = 0.02
10-day vs. SOC: *P* = 0.18

Day 14 – Clinical Status

5-day vs. SOC: *P* = 0.03
10-day vs. SOC: *P* = 0.03

Day 28 – Clinical Status

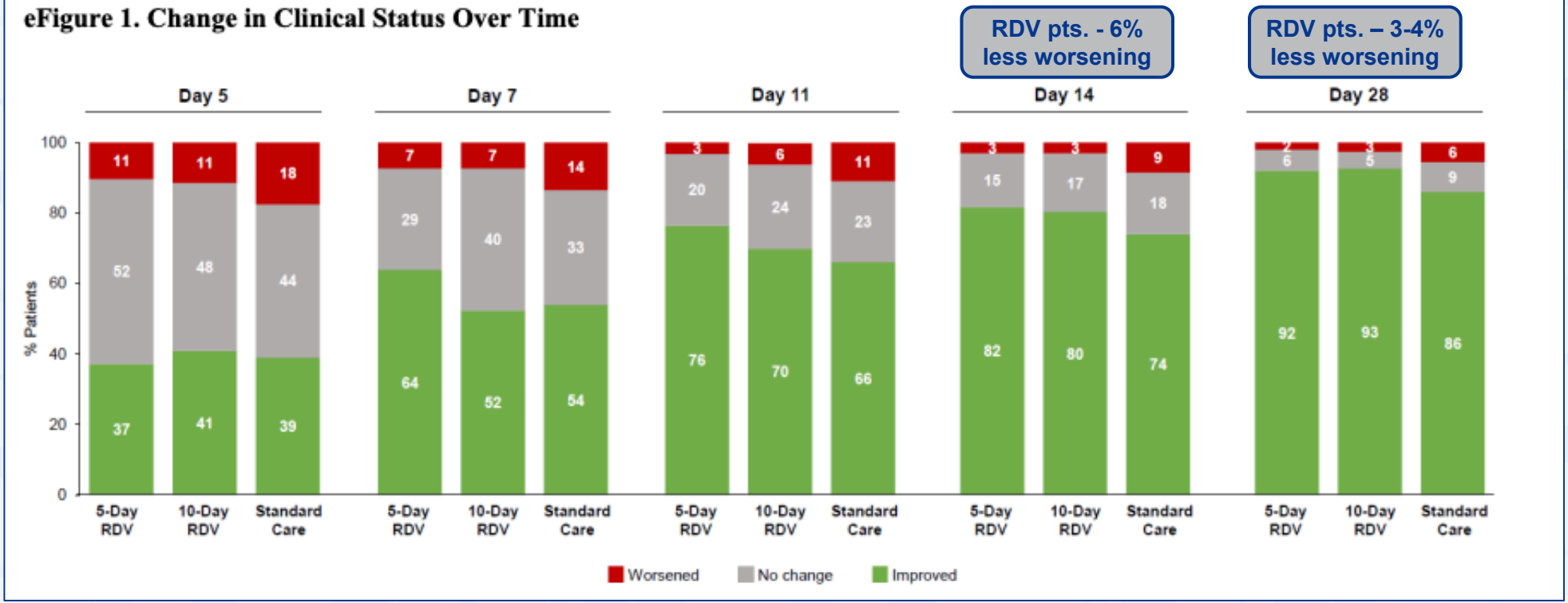
5-day vs. SOC: *P* = 0.08
10-day vs. SOC: *P* = 0.03

OR = odd's ratio; Wilcoxon rank-sum test used if odds assumption not met
Non-primary analyses should be interpreted as exploratory
Type I error risk, multiple comparisons without correction

Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

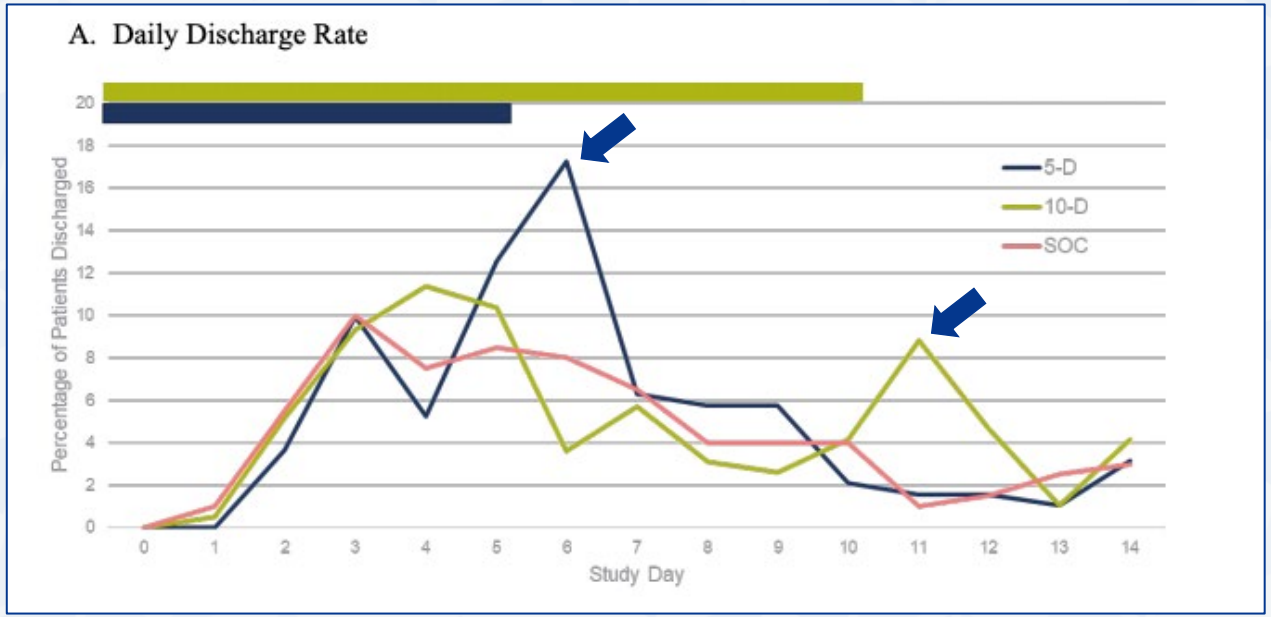
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

eFigure 1. Change in Clinical Status Over Time



Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

SIMPLE-2 Moderate – 10d vs. 5d vs. SOC



Open-label, lack of matching placebo

Daily discharge rates higher day after therapy completion

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SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Take home points:

- Significant improvement day 11 status with 5-day vs. SOC
  - Not seen with 10-day group; open-label design potential influence
- Lower disease progression with remdesivir (consistent with ACTT-1)
- Low incidence of progression to severe disease/mortality overall (≤2%)
- Safety
  - Any AE higher in 10-day (59%) vs. 5-day (51%) vs. SOC (47%)
  - Similar grade ≥ 3 (12% vs. 10% vs. 12%)
  - Low remdesivir discontinuation (4% vs. 2%)

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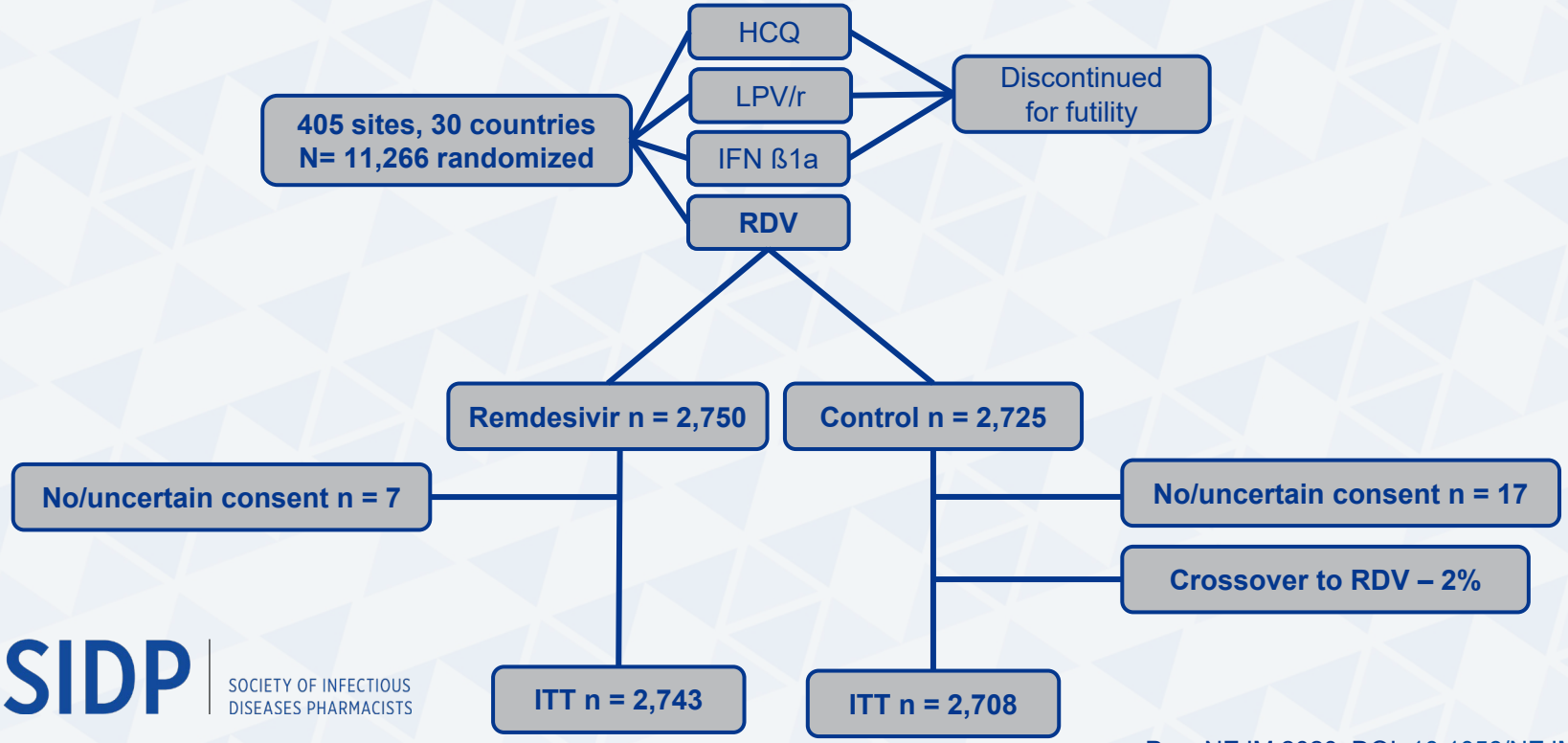
Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

WHO Solidarity – RDV Arm



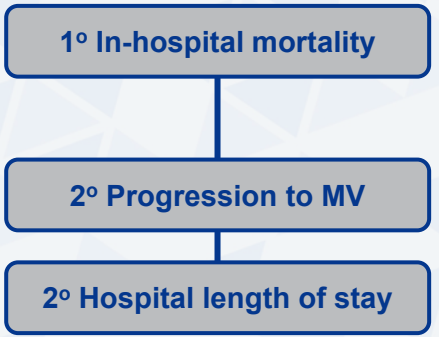
SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

WHO Solidarity – RDV Arm

Characteristic	RDV (n = 2,743)	SOC (n=2,708)
Age < 70 yr – n (%)	2,243 (81.8)	2,239 (82.6)
Age ≥ 70 yr – n (%)	500 (18.2)	469 (17.3)
Male sex – no. (%)	1,706 (62.1)	1,725 (63.7)
Baseline Status – no. (%)[&]		
No oxygen at entry	661 (24.1)	664 (24.5)
On oxygen at entry	**1,828 (66.6)**	**1,811 (66.8)**
Already ventilated	254 (9.2)	233 (8.6)
Steroids	1,310 (47.8)	1,288 (47.6)
Convalescent Plasma	52 (1.9)	58 (2.1)

Common comorbidities: diabetes (25.2%), cardiovascular disease (20.8%), hypertension (5.4%)



MV = mechanical ventilation

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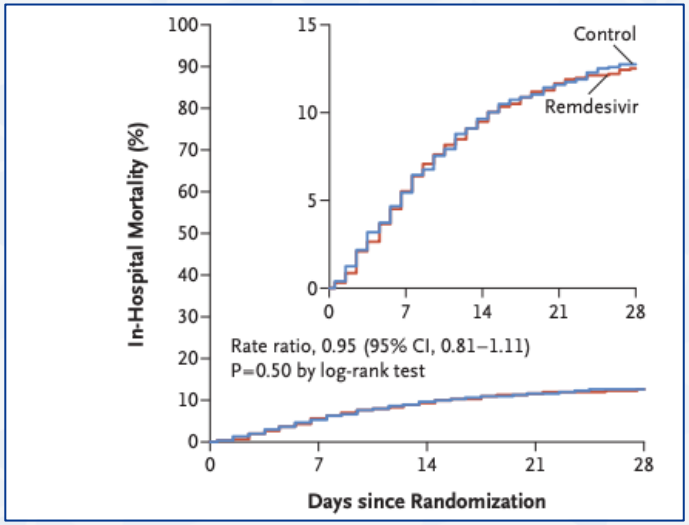
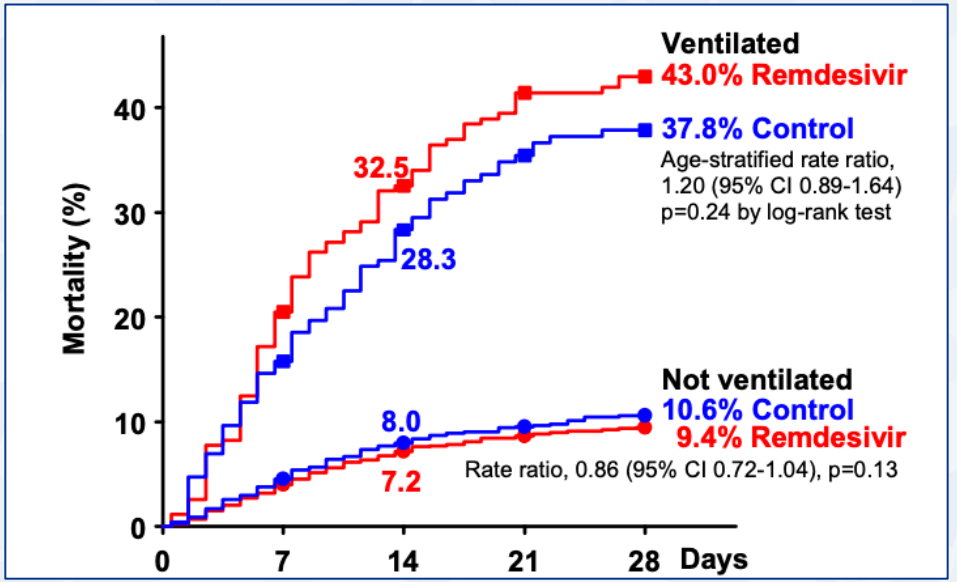
Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

WHO Solidarity – RDV Arm

Overall Population



By Ventilation Status



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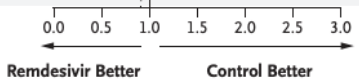
Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

WHO Solidarity – RDV Arm

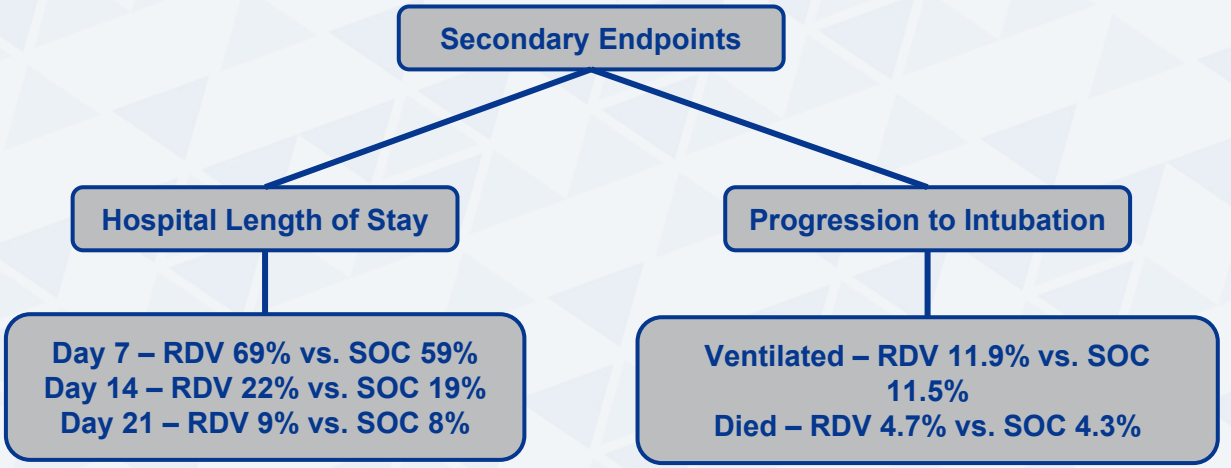
Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (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



Pan; NEJM 2020.

WHO Solidarity – RDV Arm

Remdesivir conferred no benefit towards reducing hospital length of stay or progression to intubation.



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Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

WHO Solidarity – RDV Arm

Take home points:

- Largest trial to date
  - Fivefold larger than ACTT-1
  - Open-label design (risk of bias)
- No benefit of remdesivir on mortality
  - Meta-analysis lower severity subgroup potential benefit
- No benefit observed for hospital duration or intubation rate

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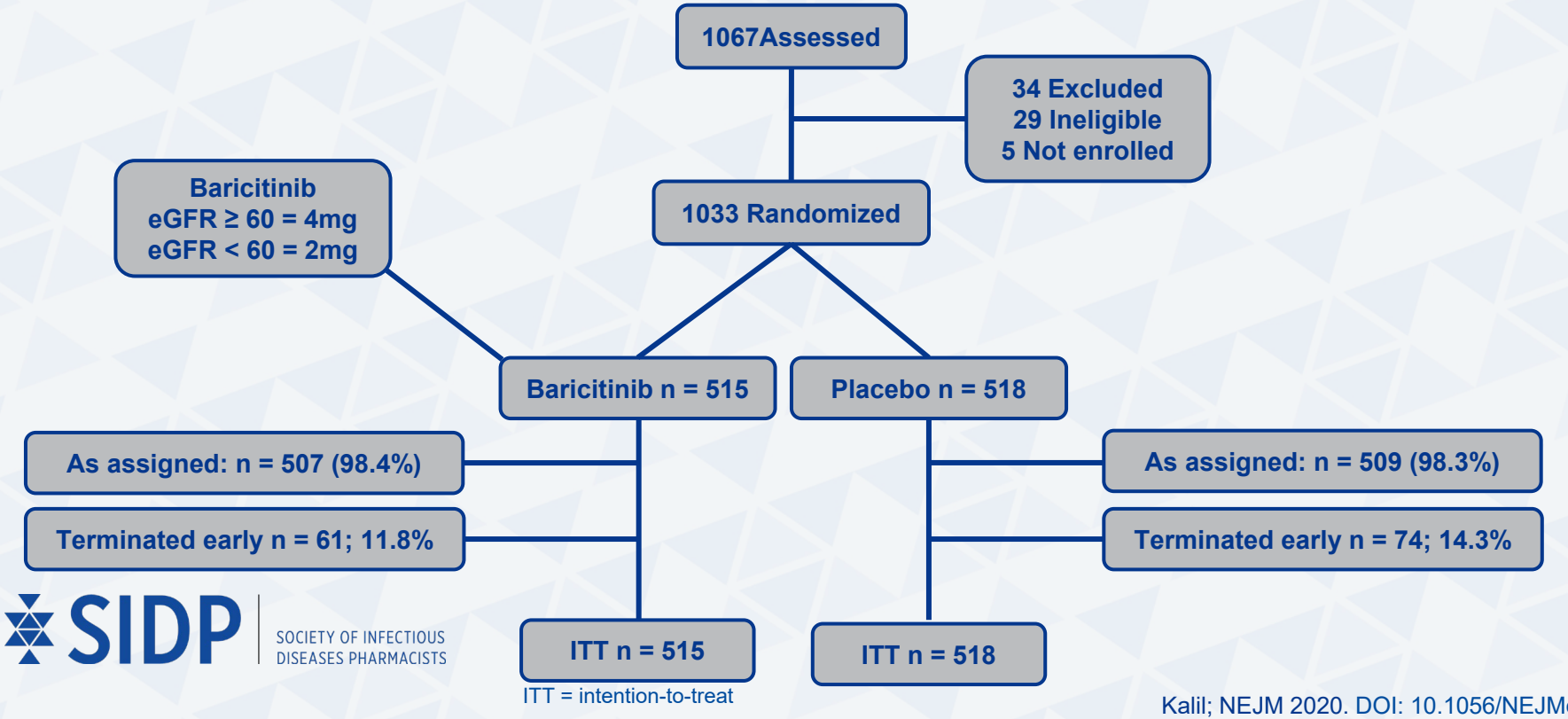
Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

Adaptive COVID Treatment Trial (ACTT-2)



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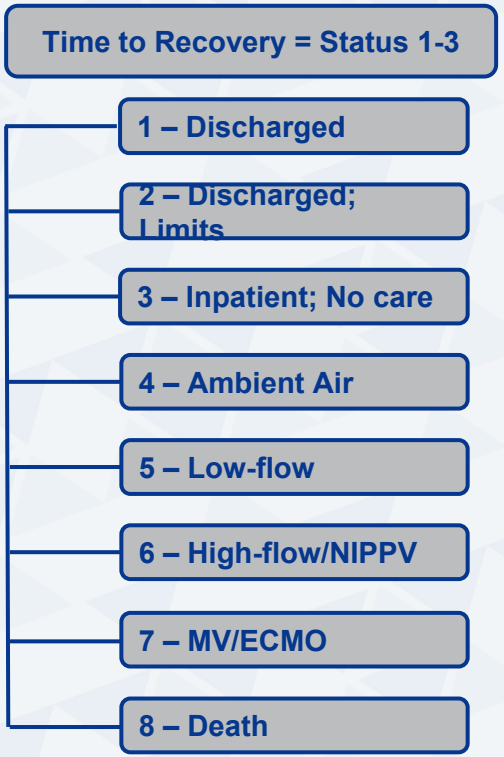
Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

Characteristic	Baricitinib (n = 515)	Placebo (n = 518)
Mean age (SD) – yr	55.0 (15.4)	55.8 (16.0)
Male sex – no. (%)	319 (61.9)	333 (64.3)
Median Sx (IQR) – days	8 (5-10)	8 (5-11)
Comorbidities ≥ 2* – no. (%)	284 (57.3)	285 (57.2)
Corticosteroids	87 (16.9)	104 (20.0)
Baseline Status – no. (%)		
Baseline – 4 (Ambient Air)	70 (13.6)	72 (13.9)
Baseline – 5 (Low-flow)	**288 (55.9)**	**276 (53.3)**
Baseline – 6 (High-flow)	**103 (20)**	**113 (21.8)**
Baseline – 7 (MV/ECMO)	54 (10.7)	57 (11.0)



NIPPV = non-invasive positive pressure ventilation

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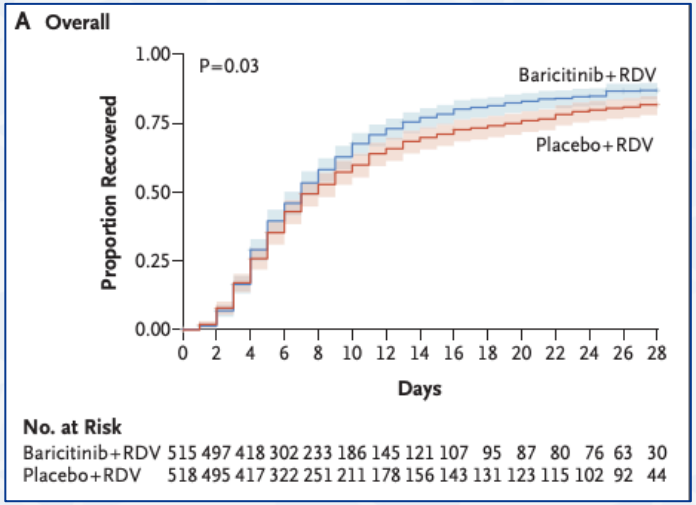
Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

Time to Recovery

Baricitinib 7 d vs. Placebo 8 d
RR 1.16 (95%CI 1.01-1.32; P=0.03)



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Length of Stay

Baricitinib 8 d (IQR 5-15)
Placebo 8 d (IQR 5-20)

28-d Mortality

HR 0.65 (95%CI 0.39-1.09)

New MV/ECMO

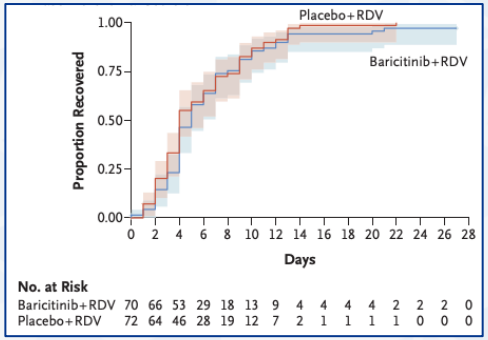
Baricitinib n = 46 (10%; 95%CI 8-13%)
Placebo n = 70 (15%; 95%CI 12-19%)

Confidence intervals unadjusted for multiplicity
Secondary analyses should not be used to infer definitive effects

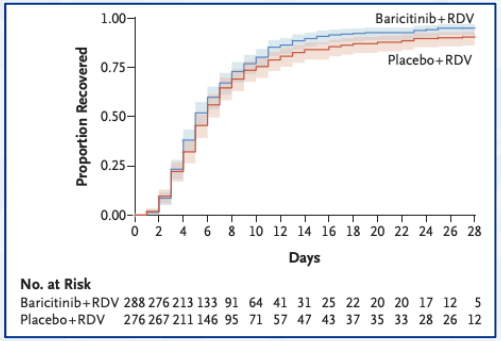
Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

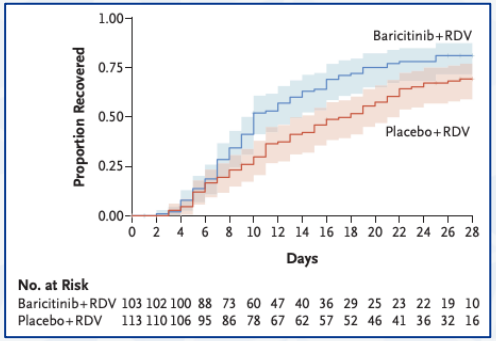
Ambient Air



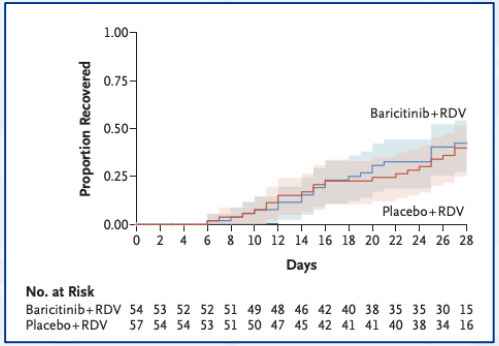
Low-flow



High-flow



MV/ECMO



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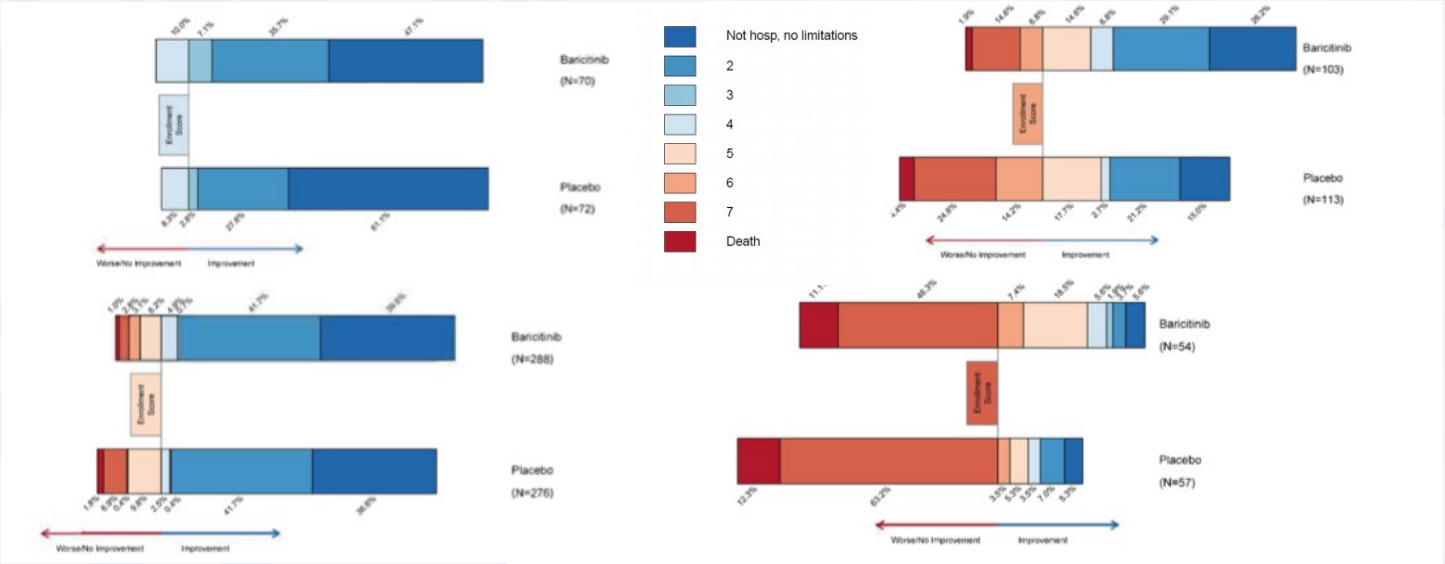
Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

Day 15 Clinical Worsening – Baricitinib vs. Placebo

Ambient Air
10% vs. 8.3%

Low-flow
6.9% vs. 9.1%



High-flow
16.5% vs. 29.2%

MV/ECMO
11.1% vs. 12.3%

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Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

Generally well tolerated; All AEs/SAEs significantly lower in baricitinib arm

Adverse Events	Baricitinib (n = 507)	Placebo (n = 509)
Adverse Events – n (%)	187 (36.9)	220 (43.2)
GFR decrease/AKI	71 (14.0)	75 (14.8)
Anemia/Hgb decrease	54 (10.6)	58 (11.4)
Transaminase increase	15 (2.9)	30 (5.9)
VTE	**21 (4.1)**	**16 (3.1)**
DVT	**11 (2.2)**	**9 (1.8)**
Serious Adverse Events	81 (16)	107 (21)
Pulmonary embolism	**5 (1)**	**2 (0.4)**
Infection	**30 (5.9)**	**57 (11.2)**

Hgb = hemoglobin; VTE = venous thromboembolism

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Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

Adaptive COVID Treatment Trial (ACTT-2)

- Statistically significant reduction in time to recovery
  - Clinical significance questionable (1-day reduction, driven by O2 requirement)
  - No effect on key secondary endpoints (length of stay, mortality)
  - Prevention of progression in high-flow patients; further investigated in ACTT-4
- Safety
  - Lower adverse event rate compared to placebo group; well-tolerated
  - No increased rates of venous thromboembolism or infectious complications in baricitinib arm

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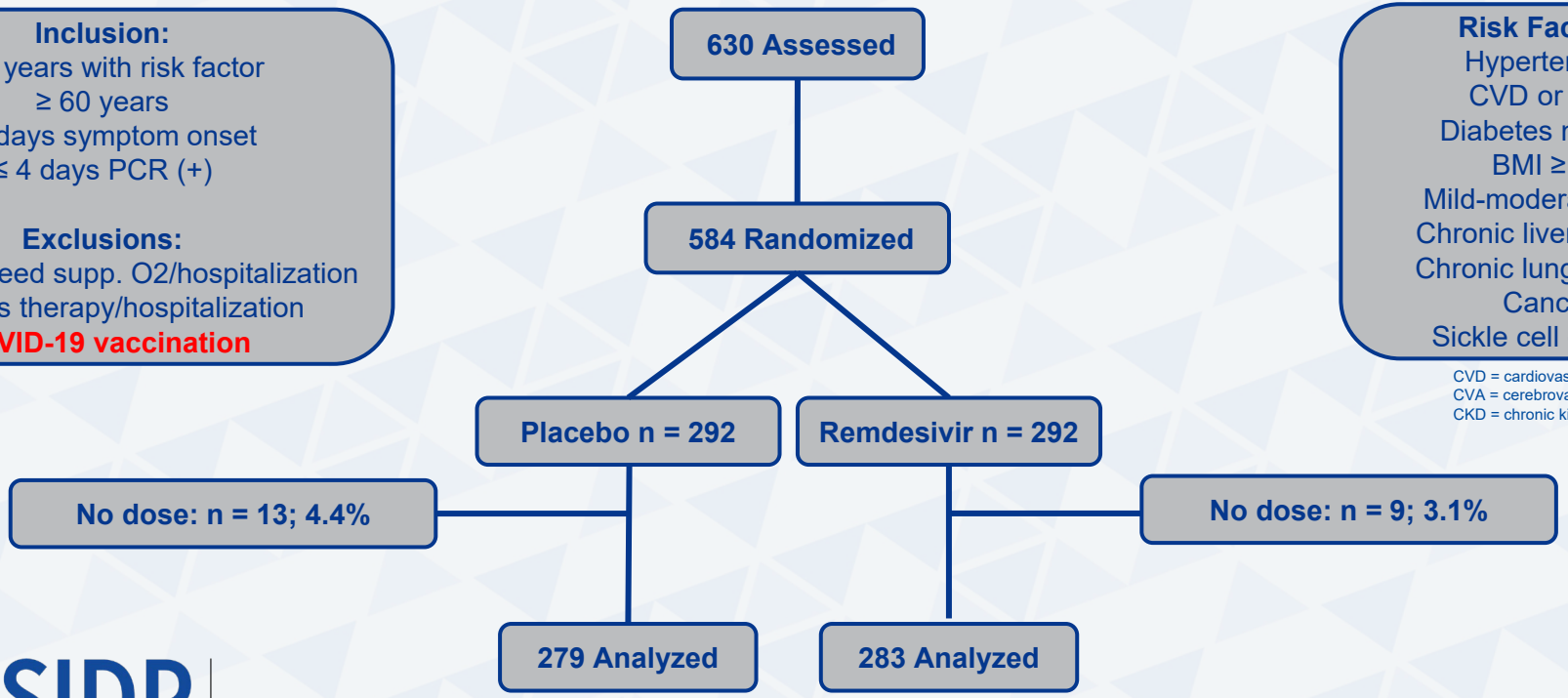
Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994

PINETREE Study – Early Outpatient Therapy

Inclusion:
≥ 12 years with risk factor
≥ 60 years
≤ 7 days symptom onset
≤ 4 days PCR (+)

Exclusions:
Perceived need supp. O2/hospitalization
Previous therapy/hospitalization
COVID-19 vaccination



Risk Factors:
Hypertension
CVD or CVA
Diabetes mellitus
BMI ≥ 30
Mild-moderate CKD
Chronic liver disease
Chronic lung disease
Cancer
Sickle cell disease

CVD = cardiovascular disease
CVA = cerebrovascular disease
CKD = chronic kidney disease

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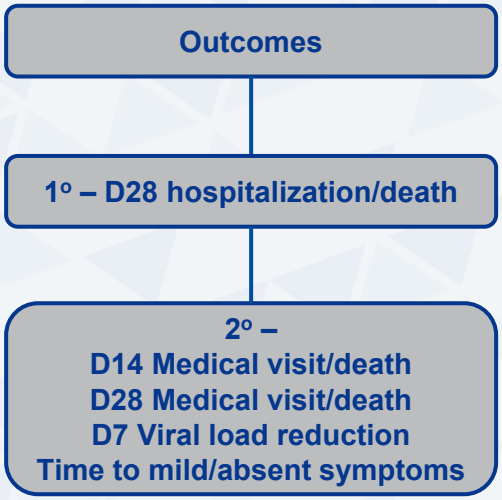
Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846

PINETREE Study – Early Outpatient Therapy

Characteristic	Baricitinib (n = 279)	Placebo (n = 283)
Mean age (SD) – yr	50 (15)	51 (15
Female sex – no. (%)	131 (47)	138 (48.8)
Body Mass Index (SD)	31.2 (6.7)	30.8 (5.8)
Median Sx (IQR) – days	5 (3-6)	5 (4-6)
Comorbidities – no. (%)		
Diabetes mellitus	173 (62)	173 (61.1)
Obesity	154 (55.2)	156 (55.1)
Hypertension	138 (49.5)	130 (45.9)
Chronic lung disease	67 (24)	68 (24)
Immune compromise	14 (5)	9 (3.2)



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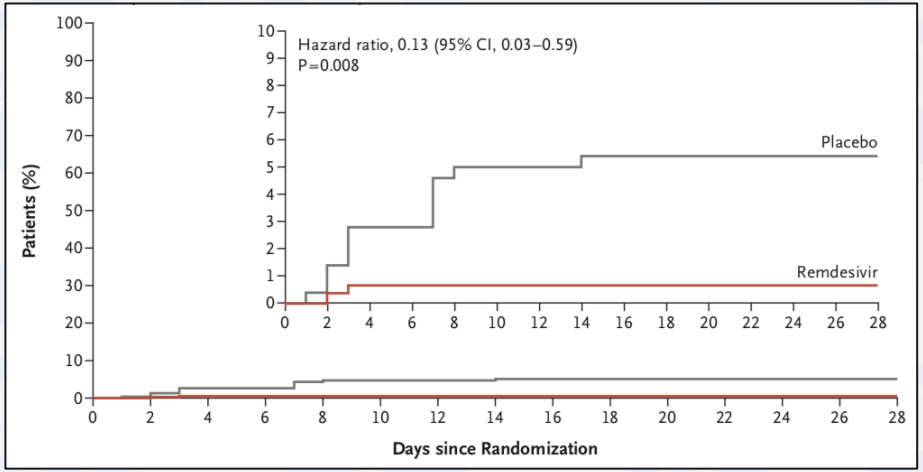
Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846

PINETREE Study – Early Outpatient Therapy

Hospitalization/Death

Remdesivir 0.7% vs. Placebo 5.3%
aHR 0.13 (95%CI 0.03-0.59; P=0.008)

Cox-proportional hazard model adjusted for SNF residence, age, location



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D14 Medical Visits/Death

Remdesivir 2/246 (0.8%)
Placebo 20/252 (7.9%)

D28 Medical Visits/Death

Remdesivir 4/246 (1.6%)
Placebo 21/252 (8.3%)

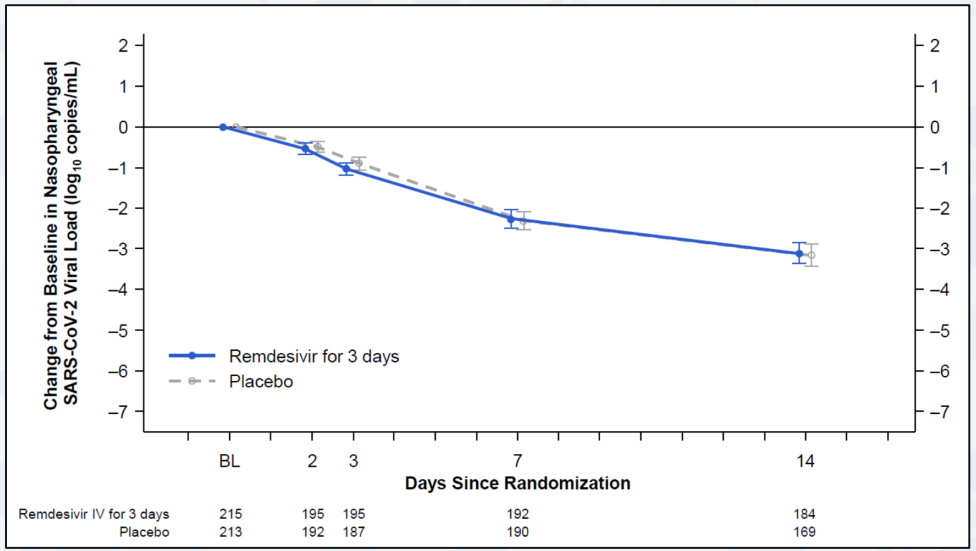
D14 Symptom Alleviation

Remdesivir 61/169 (36.1%)
Placebo 33/165 (20.0%)
RR 1.92 (95%CI 1.26-2.94)

Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846

PINETREE Study – Early Outpatient Therapy

PINETREE Study



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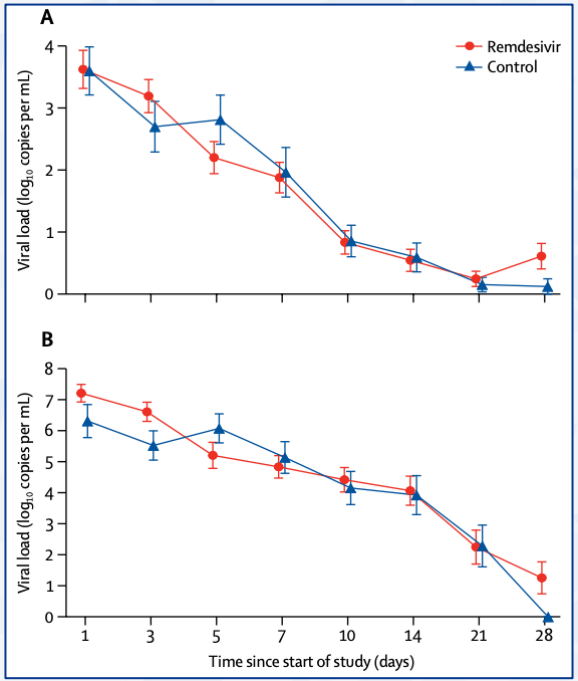
Wang *et al.*



Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846
Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9

PINETREE Study – Early Outpatient Therapy

- Statistically significant reduction COVID-19 hospitalizations
  - Nsp12 polymerase highly conserved compared to spike protein
  - Effect size would likely be diminished in vaccinated or low-risk populations; Operationally challenging
  - Immunocompromised patients underrepresented
- Significantly higher symptom resolution by day 14 with remdesivir
- No impact on virologic outcomes at day 7, similar to previous findings
- Safety
  - No new safety signals, remdesivir was well tolerated

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Gottlieb; NEJM 2021. DOI: 10.1056/NEJMoa2116846

Available (Final) Results

Variable	Lancet Severe RCT		ACTT-1		SIMPLE-1 Severe		SIMPLE-2 Moderate		
Sample, (n)	237		1062		397		596		
Severity	Hypoxia/PNA/PF < 300		Hypoxia/PNA/Supp. O2		PNA/Hypoxia; Not MV		$SpO_2 \geq 94\%$		
Sx duration, days (IQR)	10 (9-12)		9 (6-12)	9 (7-13)	8 (5-11)	9 (6-12)	8 (5-11)	8 (5-11)	9 (6-11)
Intervention	10-day	PBO	10-day	PBO	5-day	10-day	10-day	5-day	SOC
Mortality (28d), (%)	14	13	11.4	15.2	8**	11**	2	1	2
TTCR (days)	21	23	10	15	10	11	8	6	7
AEs Discontinue Tx, n (%)	18 (12)	4 (5)	52 (9.6)	70 (13.4)	9 (5)	20 (10)	8 (4)	4 (2)	N/A

Sx = symptoms; TTCR = time to clinical recovery; AE = adverse effects; Tx = treatment
**14-day mortality data; *Recovery defined differently across trials

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Wang; Lancet 2020. DOI: 10.1016/S0140-6736(20)31022-9
Beigel; NEJM 2020. DOI: 10.1056/NEJMoa2007764
Goldman; NEJM 2020. DOI: 10.1056/NEJMoa2015301
Spinner; *JAMA* 2020. DOI:10.1001/jama.2020.16349

Available Results

Variable	SOLIDARITY		ACTT-2	
Sample, (n)	5451		1033	
Severity	Hospitalized		Hypoxia/PNA/Supp. O2	
Sx duration, days (IQR)	Unspecified		8 (5-10)	8 (5-11)
Intervention	10-day	SOC	RDV + bari	RDV + pbo
Mortality (28d), (%)	12.5*	12.7*	5.1	7.8
TTCR (days)	--	--	7	8
AEs Discontinue Tx, n (%)	--	--	23 (4.4)	43 (8.3)

Sx = symptoms; TTCR = time to clinical recovery; AE = adverse effects; Tx = treatment; SOC = standard of care
*SOLIDARITY: In-hospital mortality;

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Kalil; NEJM 2020. DOI: 10.1056/NEJMoa2031994
Pan; NEJM 2020. DOI: 10.1056/NEJMoa2023184

Clinical Summary

- Remdesivir significantly reduces time to clinical recovery
  - Benefit most apparent in baseline low-flow patients; modest benefit for moderate disease
  - Minimal/no benefit observed in ≥ high-flow; Longer follow-up data needed
- No mortality benefit in overall population
  - Possible benefit in lower risk groups (patients requiring low-flow)
- Data not definitively supportive of 10-day symptom cutoff, earlier therapy plausibly better
- In patients who derive benefit, 5-days = 10-days
- Early outpatient therapy significantly reduces COVID-19 hospitalizations
  - Data in unvaccinated, symptomatic patients at risk for disease progression
- Serious and non-serious adverse events similar/lower than placebo
  - Well-tolerated overall

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Updates Log

1. 3/24/2020 – Original version posted
2. 4/5/2020 – Community transmission case report; ongoing trial info updated
3. 4/12/2020 – Compassionate use case series added; ongoing trial info updated
4. 4/17/2020 – Updated trial info
5. 4/29/2020 – Lancet Severe Trial, NIAID/SIMPLE prelim data, Updated trial info
6. 5/1/2020 – Emergency Use Authorization
7. 6/6/2020 – ACTT-1, SIMPLE-1, SIMPLE-2 top-line results, trials updated
8. 7/2020 – RDV/HCQ interaction, Phase 2/3 peds
9. 9/5/2020 – SIMPLE-2 results, EUA expansion, updated trial info
10. 10/16/2020 – Additional MOA, Updated *in vitro* data, resistance, SARS-CoV-2 animal data, Final ACTT-1, Solidarity, clinical trials data
11. 12/14/2020 – ACTT-2, SOLIDARITY final results
12. 12/24/2021 – PINETREE results

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Questions

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