Remdesivir (GS-5734)

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

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Remdesivir (GS-5734)

Mechanism of Action: Interference with viral RNA-dependent RNA polymerase; delayed chain termination of viral RNA transcription

Status: Investigational, COVID-19 Phase III trials ongoing

Formulation: Intravenous only

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

*Optimal duration currently under investigation
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog
Remdesivir Structure Activity Relationship

C-Adenosine Analog

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir
Neutral charge, bypasses rate limiting step

Siegel; ACS 2017.
Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog
Monophosphoramide 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir

Society of Infectious Diseases Pharmacists

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir
1’Cyano modification confers selectivity

Siegel; ACS 2017.
**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**: Phosphoramide prodrug activated by esterases; CYP3A4 substrate

- **Elimination**: Renal 63%, biliary 27.8%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remdesivir (GS-5734)</th>
<th>Nucleoside Metabolite (GS-441524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>-</td>
<td>2.75-4 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.84-1.04 hr</td>
<td>20.4-25.3 hr</td>
</tr>
</tbody>
</table>

*Personal Communication, Gilead; 3/13/2020.*
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
  • Constipation
  • Dyspepsia
  • Extremity pain
  • Headache
  • Nausea

• Ebola RCT
  • Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola
Safety

- Multiple-dose, 5-14 days
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### Sulfobutylether-beta Cyclodextrin (SBECO)

- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophylized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g
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
- Constipation
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- Headache
- Nausea
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  - Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola

Sulfobutylether-beta Cyclodextrin (SBECO)
- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophilized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g

Does NOT meet NIOSH/ASHP criteria for hazardous compound
Consult updated pharmacy instructions from Gilead for additional information

Drug Interactions

In vitro Antagonism with Chloroquine

The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC₅₀ values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

### In vitro Activity

<table>
<thead>
<tr>
<th>Filoviridae</th>
<th>Paramyxoviridae</th>
<th>Pneumoviridae</th>
<th>Orthocoronaviridae</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Ebola</td>
<td>● Measles</td>
<td>● Respiratory Syncytial Virus</td>
<td>● HCoV-NL63</td>
</tr>
<tr>
<td>● Marburg</td>
<td>● Mumps</td>
<td>● Human Metapneumovirus</td>
<td>● HCoV-OC43</td>
</tr>
<tr>
<td></td>
<td>● Nipah</td>
<td></td>
<td>● HCoV-229E</td>
</tr>
<tr>
<td></td>
<td>● Hendra</td>
<td></td>
<td>● HCoV-HKU1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● MERS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● SARS-CoV-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● SARS-CoV-2</td>
</tr>
</tbody>
</table>

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

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Sheahan; Sci Transl Med 2017.
In vitro Activity

<table>
<thead>
<tr>
<th>Virus</th>
<th>EC50 (cells)</th>
<th>CC50 (cells)</th>
<th>Selectivity Index</th>
</tr>
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<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>0.77 µM (Vero E6)</td>
<td>&gt;100 µM (Vero E6)</td>
<td>&gt;130</td>
</tr>
<tr>
<td>SARS-CoV-1</td>
<td>0.069 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;144</td>
</tr>
<tr>
<td>MERS</td>
<td>0.074 µM (HAE)</td>
<td>&gt; 10 µM (HAE)</td>
<td>&gt;135</td>
</tr>
<tr>
<td>Ebola</td>
<td>0.086 µM (MCr)</td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells
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<td>N/A</td>
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**SARS-CoV-2 EC50**: Ribavirin 109.5 µM, Penciclovir 95.96 µM, Favipiravir 61.9 µM, Hydroxychloroquine 0.77 µM, Chloroquine 1.13-5.47 µM

Sheahan; Sci Transl Med 2017.  
Agostini; Am Soc Micro 2018.  
Yao; CID 2020.
Coronaviruses and Proofreading

Ribavirin

Penciclovir

Favipiravir

Remdesivir

Removed by proofreading

Maintains activity; high fitness cost

Agostini; mBio 2018.
Jordan; AAC 2018.
### In vivo Animal Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
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<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✓*</td>
</tr>
</tbody>
</table>

* 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.  
Sheahan; Nat Comm 2020.  
Sheahan; Sci Transl Med 2017.
## In vivo Animal Treatment

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<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV1</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Day 1)✗ (Day 2)</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✗*</td>
</tr>
<tr>
<td>Ebola</td>
<td>✓</td>
<td>✓</td>
<td>---</td>
</tr>
</tbody>
</table>

*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir; Macaques in Ebola model were euthanized if deemed clinically moribund

“A drug that inhibits viral replication may be of little use once virus replication has reached its peak...”

De Wit; PNAS 2020.
Zou; NEJM 2020.
Randomized, Controlled Ebola Trial

1:1:1:1
Stratified on cycle-threshold (i.e. viral load)
1\(^{o}\) Outcome: 28 day mortality

- **Standard of Care +**
- **ZMapp (Control)**: Triple monoclonal antibody
- **Remdesivir (RDV)**: 200 mg load, 100 mg daily x9-13d
- **REGN-EB3**: Triple monoclonal antibody
- **MAb114**: Single Ebola survivor monoclonal

Mulangu; NEJM 2019.
Randomized, Controlled Ebola Trial

- Similar duration of symptoms (~5.5 days)/viral load
  - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
  - Higher SCr/LFTs in ZMapp/RDV (sicker?)
- ZMapp and RDV arms halted; mortality signal
Randomized, Controlled Ebola Trial

• Similar duration of symptoms (~5.5 days)/viral load
  • Per day OR 1.12 (1.00-1.24)
• Baseline characteristics generally well matched
  • Higher SCr/LFTs in ZMapp/RDV (sicker?)
• ZMapp and RDV arms halted; mortality signal

Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?
Compassionate Use Case Series

61 Patients

- 8 Excluded:
  - 7 No post-baseline data
  - 1 Erroneous start date

53 Patients

- 10 days: n = 40; 75%
- 5-9 days: n = 10; 19%
- < 5 days: n = 3; 6%

Median follow-up 18 days (IQR 13-23)
Compassionate Use Case Series

61 Patients

8 Excluded:
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53 Patients

10 days: n = 40; 75%
5-9 days: n = 10; 19%
< 5 days: n = 3; 6%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>64 (48-71)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>40 (75)</td>
</tr>
<tr>
<td>Invasive ventilation – no. (%)</td>
<td>34 (64)</td>
</tr>
<tr>
<td>ECMO – no. (%)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Median Sx before RDV (IQR) – days</td>
<td>12 (9-15)</td>
</tr>
<tr>
<td>Coexisting conditions* – no. (%)</td>
<td>36 (68)</td>
</tr>
</tbody>
</table>

*Specific conditions – n (%): hypertension 13 (25), diabetes 9 (17), hyperlipidemia 6 (11), asthma 6 (11); ECMO = extracorporeal membrane oxygenation; Sx = symptoms; RDV = remdesivir
Compassionate Use Case Series

No pre-specified endpoints

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

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation
Compassionate Use Case Series

No pre-specified endpoints:
1. Discharged
2. Ambient air
3. Low-flow
4. High-flow/NIPPV
5. MV/ECMO
6. Death

Mortality:
N = 7/53 (13%)
Mean age 74.5 (range 68-79)

Improvement/Discharge:
N = 36/53 (67.9%)

Worsening:
N = 8/53 (15.1%)

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation
Compassionate Use Case Series

No pre-specified endpoints

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

Improvement/Discharge
N= 36/53 (67.9%)

Worsening
N= 8/53 (15.1%)

Mortality
N= 7/53 (13%)
Mean age 74.5 (range 68-79)

28-day/discharge/death data unavailable
N= 17/53 (32.1%)
8 MV, 1 ECMO at last time-point
### Compassionate Use Case Series

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Patients – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>32 (60)</td>
</tr>
<tr>
<td><strong>ALT/AST increase</strong></td>
<td><strong>12 (23)</strong></td>
</tr>
<tr>
<td>Renal impairment/AKI</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Multi-organ dysfunction syndrome</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Four patients discontinued for the following:
1. Worsening renal function
2. Multi-organ dysfunction
3. Transaminitis/rash
4. Transaminitis

“No new safety signals were detected in this compassionate use cohort of short-term remdesivir therapy.”

*Adverse events listed with >5% patients

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[SIDP] SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Grein; NEJM 2020.
Compassionate Use Case Series

Take home points:

• Difficult to interpret without control group
  • Natural course vs. remdesivir effects
  • Historical comparisons of limited value
  • No pre-specified endpoints
  • Median start day 12 of illness; no quantitative PCR to evaluate viral load progression

• High risk of bias
  • Selection – patients screened for compassionate use
  • Sampling – unclear if consecutive patients, not all compassionate use patients included
  • Reporting – 8 patients excluded for erroneous/lack of data, high proportion without endpoints

• Safety profile consistent with previous data
  • Toxicity vs. underlying disease
Severe RCT in China

255 Patients

18 Excluded
14 Ineligible
4 Withdrew

236 Patients

Target Enrollment
n=453
Terminated Early

Placebo n = 78
Remdesivir n = 158

No dose: n = 3; 1.8%
< 5 days: n = 5; 3.2%
PP: n = 150; 94.9%

PP = Per protocol
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>65 (56-71)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>140 (59.3)</td>
</tr>
<tr>
<td>Low-flow O₂ – no. (%)</td>
<td>129 (82)</td>
</tr>
<tr>
<td>HFNC/MV/ECMO – no. (%)</td>
<td>28 (18)</td>
</tr>
<tr>
<td>NEWS-2 – (IQR)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>10 (9-12)</td>
</tr>
<tr>
<td>Coexisting conditions* – no. (%)</td>
<td>167 (70.7)</td>
</tr>
<tr>
<td>Corticosteroids – no. (%)</td>
<td>91 (38.6)</td>
</tr>
</tbody>
</table>

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%)

Wang; Lancet 2020.
Severe RCT in China

Improvement = 2-pt Reduction

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

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

Time to Improvement

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

Wang; Lancet 2020.
Severe RCT in China

Improvement = 2-pt Reduction

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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)

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 -1.1 to 10.3)

Wang; Lancet 2020.
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.

**Viral Load**

![Graphs](image-url)
Severe RCT in China

Placebo-controlled data

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

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

Wang; Lancet 2020.
Severe RCT in China

Take home points:
• Control group!
  • Highest quality data to date
• 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

Wang; Lancet 2020.
Adaptive COVID Treatment Trial (ACTT-1)

*Preliminary Report

1107 Assessed
- 44 Excluded
  - 25 Ineligible
  - 19 Not enrolled

1063 Randomized
- 1063 Randomized

Placebo n = 522
- No dose: n = 4; 0.7%
- Completed: n = 340; 65.3%

Remdesivir n = 541
- No dose: n = 10; 1.8%
- Completed: n = 391; 72.6%

521 Analyzed
538 Analyzed

Completed: n = 391; 72.6%

Beigel; NEJM 2020.
### Adaptive COVID Treatment Trial (ACTT-1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remdesivir (n = 541)</th>
<th>Placebo (n = 522)</th>
</tr>
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<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>58.6 (14.6)</td>
<td>59.2 (15.4)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>352 (65.1)</td>
<td>332 (63.6)</td>
</tr>
<tr>
<td>Median Sx (IQR) – days</td>
<td>9 (6-12)</td>
<td>9 (7-13)</td>
</tr>
<tr>
<td>Comorbidities ≥ 2* – no. (%)</td>
<td>245 (52.5)</td>
<td>234 (51.7)</td>
</tr>
<tr>
<td>Baseline Status – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – 4 (Ambient Air)</td>
<td>67 (12.4)</td>
<td>60 (11.5)</td>
</tr>
<tr>
<td>Baseline – 5 (Low-flow)</td>
<td>222 (41.0)</td>
<td>199 (38.1)</td>
</tr>
<tr>
<td>Baseline – 6 (High-flow)</td>
<td>98 (18.1)</td>
<td>99 (19.0)</td>
</tr>
<tr>
<td>Baseline – 7 (MV/ECMO)</td>
<td>125 (23.1)</td>
<td>147 (28.2)</td>
</tr>
</tbody>
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**MV** = mechanical ventilation; **Sx** = symptoms,
*Most common = HTN (49.6%), obesity (37.0%), diabetes (29.7%)
## Adaptive COVID Treatment Trial (ACTT-1)

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<td>234 (51.7)</td>
</tr>
<tr>
<td><strong>Baseline Status – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline – 4 (Ambient Air)</td>
<td>67 (12.4)</td>
<td>60 (11.5)</td>
</tr>
<tr>
<td>Baseline – 5 (Low-flow)</td>
<td>222 (41.0)</td>
<td>199 (38.1)</td>
</tr>
<tr>
<td>Baseline – 6 (High-flow)</td>
<td>98 (18.1)</td>
<td>99 (19.0)</td>
</tr>
<tr>
<td>Baseline – 7 (MV/ECMO)</td>
<td>125 (23.1)</td>
<td>147 (28.2)</td>
</tr>
</tbody>
</table>

MV = mechanical ventilation; Sx = symptoms, *Most common = HTN (49.6%), obesity (37.0%), diabetes (29.7%)

### Time to Recovery = Status 1-3

1 – Discharged
2 – Discharged; Limits
3 – Inpatient; No care
4 – Ambient Air
5 – Low-flow
6 – High-flow/NIPPV
7 – MV/ECMO
8 – Death

NIPPV = non-invasive positive pressure ventilation
Adaptive COVID Treatment Trial (ACTT-1)

Time to Recovery
Remdesivir 11 d vs. Placebo 15 d
RR 1.32 (95%CI 1.12-1.55; P<0.001)

Time to Recovery
Adjusted for baseline clinical status
RR 1.31 (95%CI 1.12-1.57)

Beigel; NEJM 2020.
Adaptive COVID Treatment Trial (ACTT-1)

**Time to Recovery**

Remdesivir 11 d vs. Placebo 15 d
RR 1.32 (95%CI 1.12-1.55; P<0.001)

### Recovery Rate Ratio (95% CI)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Recovery Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1059</td>
<td>1.32 (1.12–1.55)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>844</td>
<td>1.33 (1.11–1.59)</td>
</tr>
<tr>
<td>Europe</td>
<td>163</td>
<td>1.40 (0.90–2.16)</td>
</tr>
<tr>
<td>Asia</td>
<td>52</td>
<td>1.20 (0.65–2.22)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>563</td>
<td>1.39 (1.12–1.73)</td>
</tr>
<tr>
<td>Black</td>
<td>219</td>
<td>1.14 (0.81–1.61)</td>
</tr>
<tr>
<td>Asian</td>
<td>134</td>
<td>1.04 (0.68–1.57)</td>
</tr>
<tr>
<td>Other</td>
<td>143</td>
<td>1.89 (1.15–3.10)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>247</td>
<td>1.23 (0.88–1.72)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>748</td>
<td>1.33 (1.10–1.61)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;60 yr</td>
<td>119</td>
<td>1.03 (1.31–3.15)</td>
</tr>
<tr>
<td>60 to &lt;65 yr</td>
<td>558</td>
<td>1.16 (0.94–1.44)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>382</td>
<td>1.37 (1.02–1.83)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>682</td>
<td>1.31 (1.07–1.59)</td>
</tr>
<tr>
<td>Female</td>
<td>377</td>
<td>1.38 (1.05–1.81)</td>
</tr>
<tr>
<td>Symptoms duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 days</td>
<td>664</td>
<td>1.28 (1.05–1.57)</td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>380</td>
<td>1.38 (1.05–1.81)</td>
</tr>
<tr>
<td>Baseline ordinal score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (not receiving oxygen)</td>
<td>127</td>
<td>1.38 (0.94–2.03)</td>
</tr>
<tr>
<td>5 (receiving oxygen)</td>
<td>421</td>
<td>1.47 (1.17–1.84)</td>
</tr>
<tr>
<td>6 (receiving high-flow oxygen or noninvasive mechanical ventilation)</td>
<td>197</td>
<td>1.20 (0.79–1.81)</td>
</tr>
<tr>
<td>7 (receiving mechanical ventilation or ECMO)</td>
<td>272</td>
<td>0.95 (0.64–1.42)</td>
</tr>
</tbody>
</table>

*Confidence intervals unadjusted for multiplicity; Should not be used to infer treatment effects
“A test of interaction of treatment with baseline score on the ordinal scale was not significant.”
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 Clinical Worsening – Remdesivir vs. Placebo

Ambient Air
8.3% vs. 15.7%

Low-flow
8.7% vs. 21.8%

High-flow
25.4% vs. 33.7%

MV/ECMO
13.9% vs. 16.5%
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 – Clinical Status*
OR 1.50 (95% CI 1.18 to 1.91)

*Original primary endpoint

Figure S5. Histogram of ordinal scores at Day 15 by treatment arm
Adaptive COVID Treatment Trial (ACTT-1)

Day 15 – Clinical Status
OR 1.50 (95%CI 1.18 to 1.91)

Mortality
KM Estimate 7.1% vs. 11.9%
HR 0.70 (95%CI 0.47-1.04)

KM = Kaplan-Meier

Beigel; NEJM 2020.
## Adaptive COVID Treatment Trial (ACTT-1)

Generally well tolerated overall

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

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Remdesivir (n = 541)</th>
<th>Placebo (n = 522)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious – n (%)</strong></td>
<td>114 (21.1)</td>
<td>141 (27)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7 (1.3)</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Hypoxia/resp. failure</td>
<td>13 (2.4)</td>
<td>15 (2.9)</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>6 (1.1)</td>
<td>15 (2.9)</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>156 (28.8)</td>
<td>172 (33.0)</td>
</tr>
<tr>
<td>Anemia/Hgb decrease</td>
<td>43 (7.9)</td>
<td>47 (9.0)</td>
</tr>
<tr>
<td><strong>Acute kidney injury</strong></td>
<td>40 (7.4)</td>
<td>38 (7.3)</td>
</tr>
<tr>
<td><strong>AST/ALT elevation</strong></td>
<td>22 (4.1)</td>
<td>31 (5.9)</td>
</tr>
<tr>
<td>Lymphocyte decrease</td>
<td>13 (2.4)</td>
<td>18 (3.4)</td>
</tr>
</tbody>
</table>

Hgb = hemoglobin

Beigel; NEJM 2020.
Adaptive COVID Treatment Trial (ACTT-1)

Take home points:

• 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 since symptom onset

• Mortality
  • No statistically significant reduction in mortality; Arguably clinically significant reduction

• Preliminary Results
  • 301 patients continuing trial/not recovered

• Safety
  • Lower adverse event rate compared to placebo group; well-tolerated

Beigel; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

408 Screened
397 Started

5 Ineligible
1 Discharged
5 No treatment

Excluded
MV/ECMO
MODS

MODS = multi-organ dysfunction syndrome

5-Day n = 200
10-Day n = 197

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

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

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

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

14 Day Clinical Status

- P=0.14
- Stratified Wilcoxon rank-sum
- Adjusted for baseline clinical status

1 – Death
2 – MV/ECMO
3 – High-flow/NIV
4 – Low-flow
5 – Ambient air; care
6 – Ambient air; no care
7 – Discharged

MV = mechanical ventilation; NIV = non-invasive ventilation
SIMPLE-1 Severe – 5 vs. 10 days

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)

MV = mechanical ventilation; NIV = non-invasive ventilation

1 – Death
2 – MV/ECMO
3 – High-flow/NIV
4 – Low-flow
5 – Ambient air; care
6 – Ambient air; no care
7 – Discharged

Goldman; NEJM 2020.
SIMPLE-1 Severe – 5 vs. 10 days

Caution:
- Post-hoc analysis
- Small subgroups
- Inconsistent trends
## SIMPLE-1 Severe – 5 vs. 10 days

### Day 14 Improvement

<table>
<thead>
<tr>
<th>No. of Patients in Oxygen-Support Group at Day 14 (%)</th>
<th>5-day course of remdesivir (N=193)*</th>
<th>10-day course of remdesivir (N=188)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invasive (N=4)</td>
<td>Noninvasive (N=49)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Invasive</td>
<td>2</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>4</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Ambient air</td>
<td>5/6</td>
<td>0</td>
</tr>
<tr>
<td>Discharged</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Improvement</td>
<td>1 (25)</td>
<td>28 (57)</td>
</tr>
</tbody>
</table>

**Improvement: ACTT-1 Placebo**

- 44.3% 58.5% 74.5% 76.6%
- 44.3% 58.5% 74.5% 76.6%
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)
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

612 Screened

596 Randomized

16 Excluded

10-Day n = 197

193 Started

73 (37.8%) Completed

Median 6 days

5-Day n = 199

191 Started

145 (75.9%) Completed

Median 5 days

SOC n = 200

Open-label

SOC = Standard care

SOC = Standard care

SpinneR; JAMA 2020.
### SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

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

Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)
### SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

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

**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**

Most common comorbidities: cardiovascular disease (55.1%), hypertension (41.5%), diabetes (38.8%)
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

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

1° = Day 11 Clinical Status
7 – Discharged
6 – Inpatient; No care
5 – Inpatient; Care
4 – Low-flow
3 – High-flow
2 – MV/ECMO
1 – Death
eFigure 1. Change in Clinical Status Over Time

- **RDV pts. - 6% less worsening**
- **RDV pts. – 3-4% less worsening**
SIMPLE-2 Moderate – 10d vs. 5d vs. SOC

Open-label, lack of matching placebo

Daily discharge rates higher day after therapy completion
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%)

SIDP
SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Spinner; JAMA 2020.
## Available Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lancet Severe RCT</th>
<th>ACTT-1</th>
<th>SIMPLE-1 Severe</th>
<th>SIMPLE-2 Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample, (n)</td>
<td>237</td>
<td>1063</td>
<td>397</td>
<td>596</td>
</tr>
<tr>
<td>Severity</td>
<td>Hypoxia/PNA/PF &lt; 300</td>
<td>Hypoxia/PNA/Supp. O2</td>
<td>PNA/Hypoxia; Not MV</td>
<td>SpO₂ ≥ 94%</td>
</tr>
<tr>
<td>Sx duration, days (IQR)</td>
<td>10 (9-12)</td>
<td>9 (6-12)</td>
<td>9 (7-13)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Intervention</td>
<td>10-day PBO</td>
<td>10-day PBO</td>
<td>5-day</td>
<td>10-day</td>
</tr>
<tr>
<td>Mortality (28d), (%)</td>
<td>14</td>
<td>13</td>
<td>7.1**</td>
<td>11.9**</td>
</tr>
<tr>
<td>TTCR (days)/Recovery* (%)</td>
<td>21 days</td>
<td>23 days</td>
<td>11 days</td>
<td>15 days</td>
</tr>
<tr>
<td>AEs Discontinue Tx, n (%)</td>
<td>18 (12)</td>
<td>4 (5)</td>
<td>36 (6.7)</td>
<td>36 (6.9)</td>
</tr>
</tbody>
</table>

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

Wang; Lancet 2020.
Beigel; NEJM 2020.
Goldman; NEJM 2020.
Spinner; JAMA 2020.

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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
• Clinically, but not statistically significant day 14 mortality reduction in ACTT-1
• Data not supportive of 10-day symptom cutoff
• In patients who derive benefit, 5-days = 10-days
• Serious and non-serious adverse events similar/lower than placebo
  • Well-tolerated overall
Emergency Use Authorization

COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19

“It is reasonable to believe Veklury (remdesivir) may be effective [...] for COVID-19 in all hospitalized adult and pediatric patients. The Agency’s review has also concluded that the known/potential benefits outweigh the known/potential risks for these uses.”
## Current Investigations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTT-3</td>
<td>NIAID</td>
<td>SpO$_2$ ≤ 94%</td>
<td>RDV + IFN β-1a vs. RDV + PCB</td>
</tr>
<tr>
<td>DisCoVeRy</td>
<td>Inserm</td>
<td>SpO$_2$ &lt; 94%</td>
<td>RDV vs. HCQ vs. IFN-ß vs. LPV/r vs. SOC</td>
</tr>
<tr>
<td>Solidarity</td>
<td>WHO</td>
<td>Hospitalized</td>
<td>RDV vs. HCQ vs. LPV/r vs. IFN-ß1a</td>
</tr>
<tr>
<td>REMDACTA</td>
<td>Roche/Gilead</td>
<td>&gt; 6L NC</td>
<td>RDV + tocilizumab vs. RDV + PCB</td>
</tr>
<tr>
<td>Outpatient RDV</td>
<td>Gilead</td>
<td>≥ 1 RF; Sx ≤ 7 d</td>
<td>RDV vs. PCB</td>
</tr>
<tr>
<td>TICO</td>
<td>NIAID</td>
<td>Hospitalized</td>
<td>RDV + LY3819253 vs. RDV + PCB</td>
</tr>
<tr>
<td>CARAVAN</td>
<td>Gilead</td>
<td>≥ 28 days to &lt; 18</td>
<td>RDV (Phase 2/3)</td>
</tr>
<tr>
<td>Inhaled RDV</td>
<td>Gilead</td>
<td>SpO$_2$ &gt; 94%</td>
<td>Inhaled RDV vs. PCB (Phase 1b/2a)</td>
</tr>
</tbody>
</table>

RDV = remdesivir; PCB = placebo; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; IFN-ß = interferon beta; Source: ClinicalTrials.gov
References

References

21. Chin-Hong, Peter (PCH_SF). We have fielded a lot of requests from around the country for our experience with getting #compassionateuse #remdesivir from #Gilead for critically ill #COVID19 pts. Pears:1)~72 hrs if approved 2)Many steps but doable 3)Model of #interprofessional ID/IPharm aloha. We are all in.” 3/16/20. Tweet.
Updates Log

3/24/2020 – Original version posted
4/5/2020 – Community transmission case report; ongoing trial info updated
4/12/2020 – Compassionate use case series added; ongoing trial info updated
4/17/2020 – Updated trial info
4/29/2020 – Lancet Severe Trial, NIAID/SIMPLE prelim data, Updated trial info
5/1/2020 – Emergency Use Authorization
6/6/2020 – ACTT-1, SIMPLE-1, SIMPLE-2 top-line results, trials updated
7/2020 – RDV/HCQ interaction, Phase 2/3 peds
9/5/2020 – SIMPLE-2 results, EUA expansion, updated trial info
Questions

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