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; premature 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

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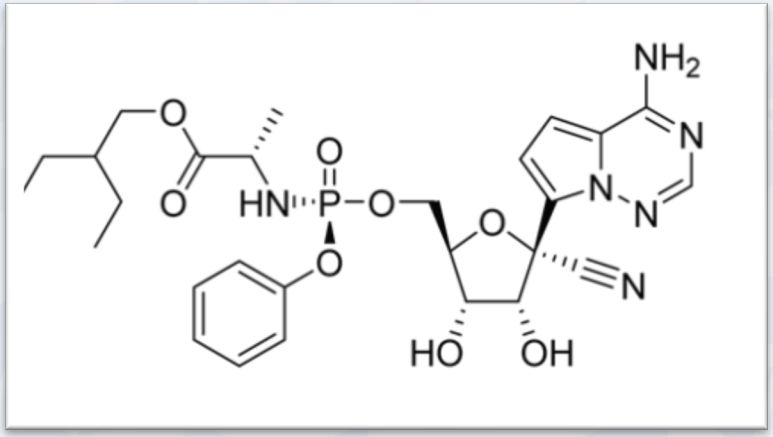
*Optimal duration currently under investigation

Tchesnokov; Viruses 2019.

Remdesivir Structure Activity Relationship



Monophosphoramidate 1'Cyano C-adenosine Nucleoside Analog

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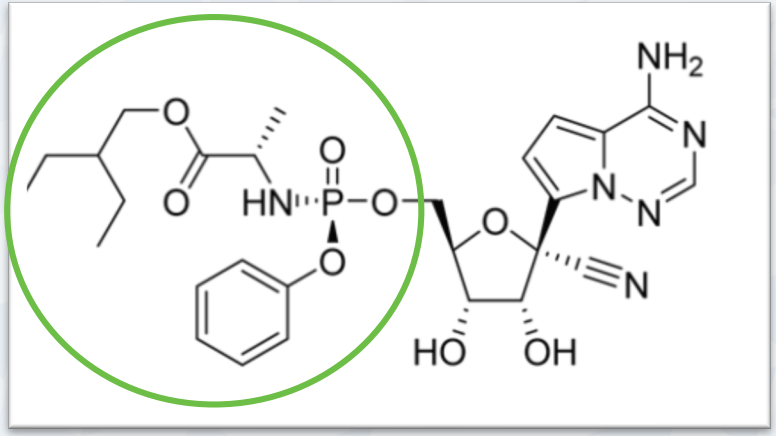
Siegel; ACS 2017.

Remdesivir Structure Activity Relationship



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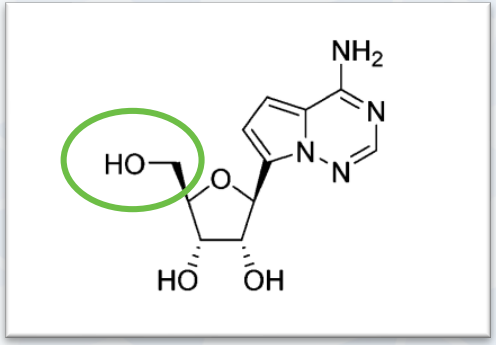
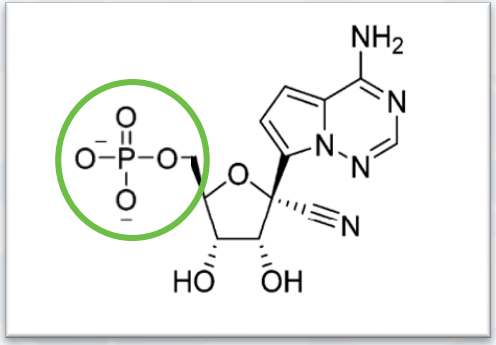
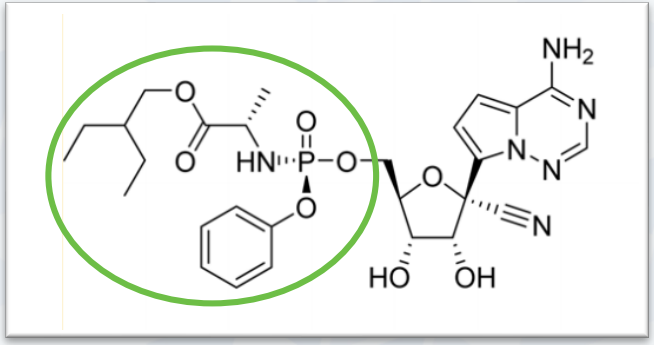


C-Adenosine Analog



Monophosphate Form



Remdesivir

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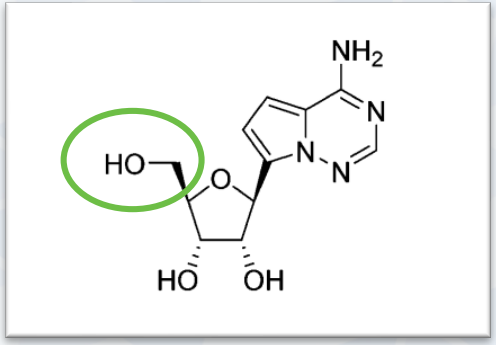
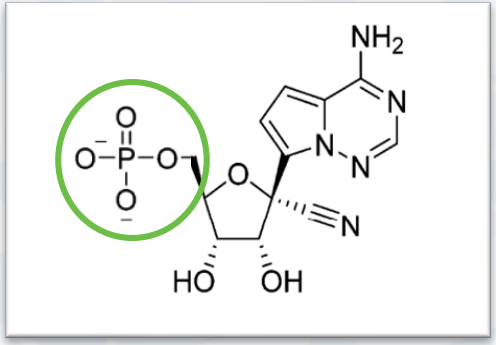


C-Adenosine Analog

Rate limiting phosphorylation



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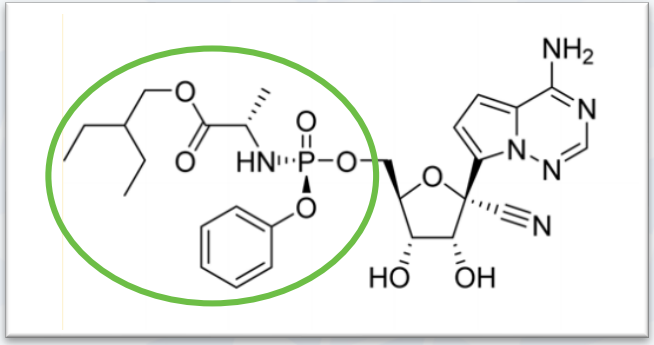

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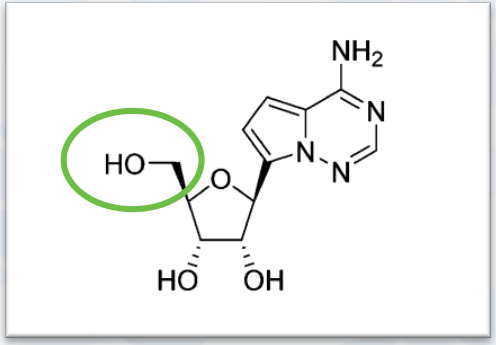

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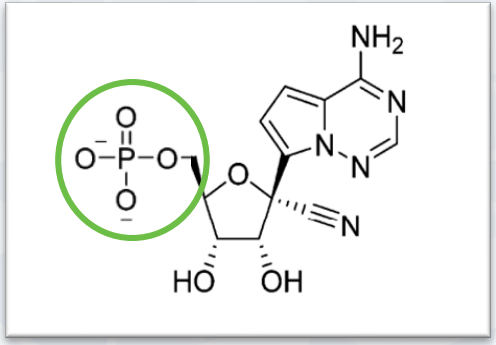
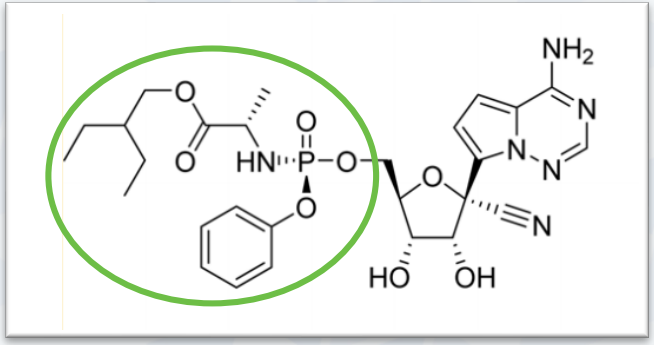


Monophosphate Form

Charge reduces permeability



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Siegel; ACS 2017.

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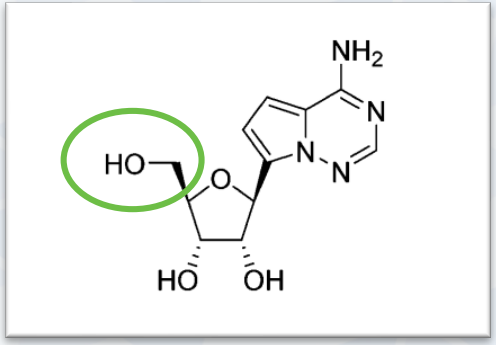

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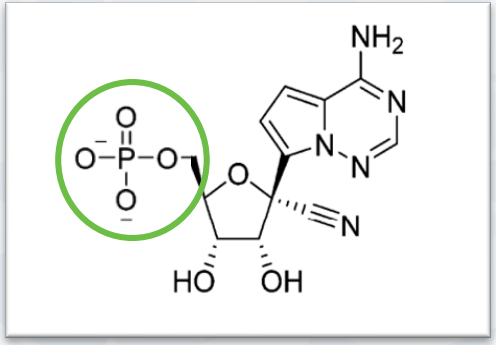

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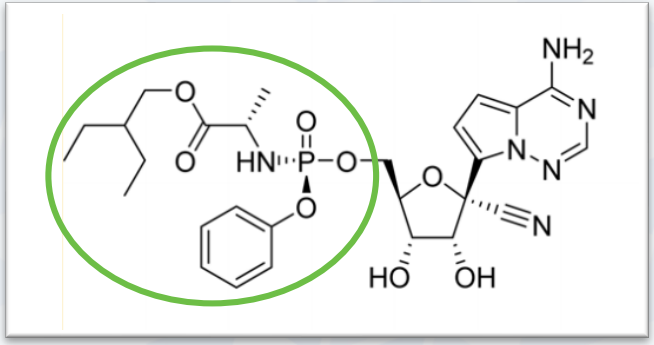

Remdesivir

Neutral charge, bypasses rate limiting step

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Siegel; ACS 2017.

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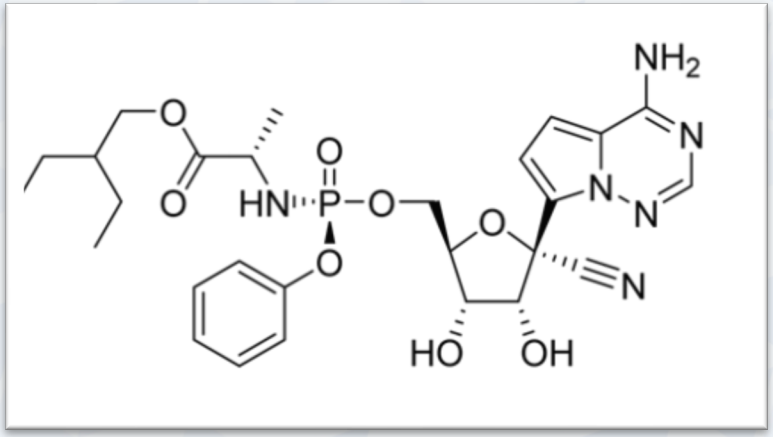

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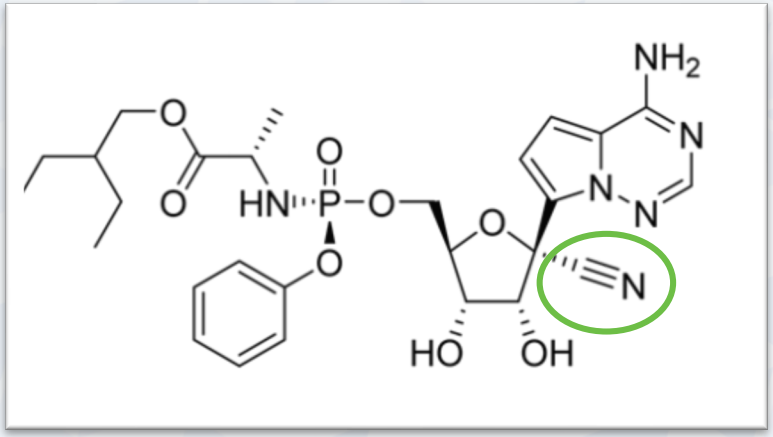

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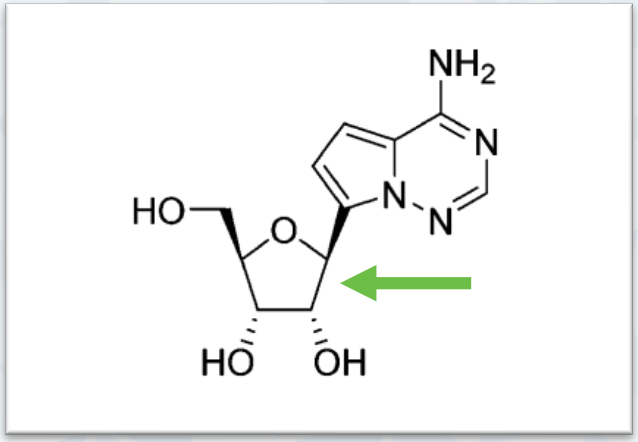
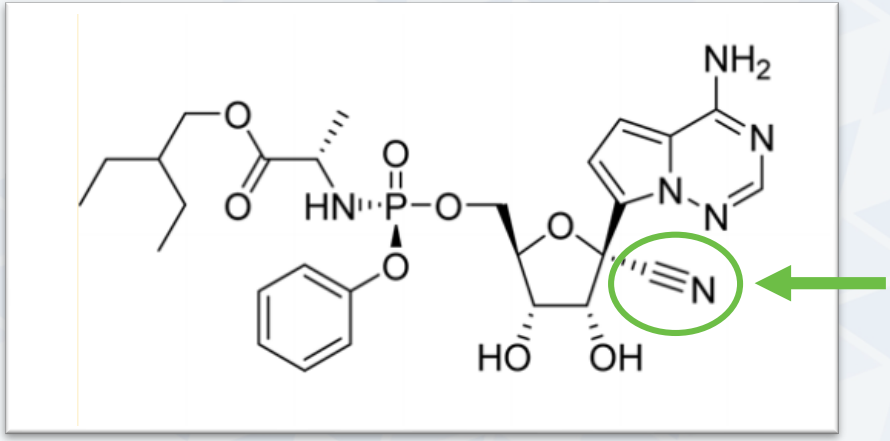


C-Adenosine Analog

Poor selectivity, highly cytotoxic



Remdesivir

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Siegel; ACS 2017.

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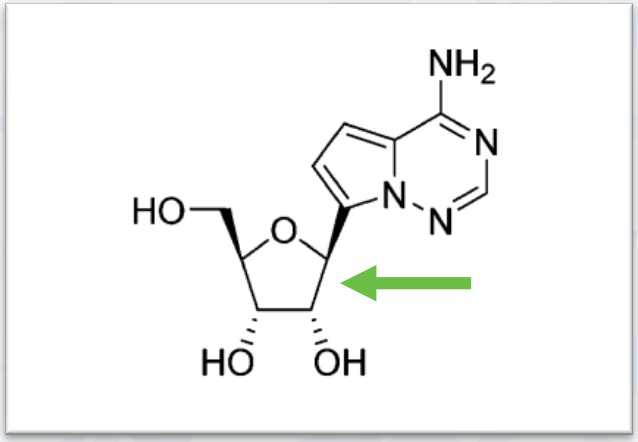

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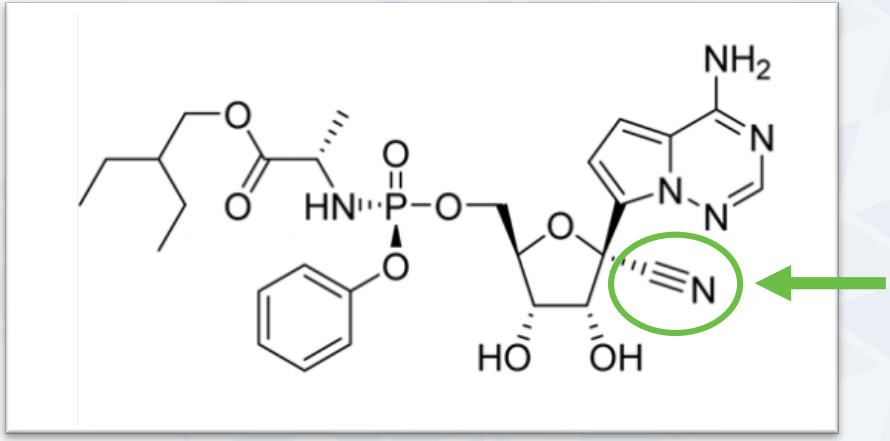

Remdesivir

1'Cyano modification confers selectivity

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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**: Phosphoramidate prodrug activated by esterases; CYP3A4 substrate
- **Elimination**: Renal 63%, biliary 27.8%

Parameter	Remdesivir (GS-5734)	Nucleoside Metabolite (GS-441524)
C_{max}	2.6 µg/mL	0.14-0.15 µg/mL
T_{max}	-	2.75-4 hr
Half-life	0.84-1.04 hr	20.4-25.3 hr

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

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Sulfobutylether-beta Cyclodextrin (SBECD)

Remdesivir 150 mg solution - **9 g**
Remdesivir 150 mg lyophylized powder - **4.5 g**
Voriconazole 400 mg - **6.4 g**

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Does **NOT** meet NIOSH/ASHP criteria for hazardous compound

Consult updated pharmacy instructions from Gilead for additional information

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Personal Communication, Gilead; 3/18/2020.

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** • **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.
Lo; Sci Rep 2017.
Sheahan; Sci Transl Med 2017.

In vitro Activity

Virus	EC50 (cells)	CC50 (cells)	Selectivity Index
SARS-CoV-2	**0.77 µM (Vero E6)**	>100 µM (Vero E6)	>130
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; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells

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Gordon; J Bio Chem 2020.
Sheahan; Sci Transl Med 2017.
Agostini; Am Soc Micro 2018.
Yao; *CID* 2020.

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SARS-CoV-1		> 10 µM (HAE)	>144
MERS		> 10 µM (HAE)	>135
Ebola		6.1 (Hep-2)	N/A

SARS-CoV-2 EC_{50}

Ribavirin 109.5 µM
Penciclovir 95.96 µM
Favipiravir 61.9 µM
Hydroxychloroquine 0.77 µM
Chloroquine 1.13-5.47 µM

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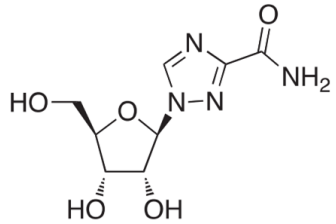
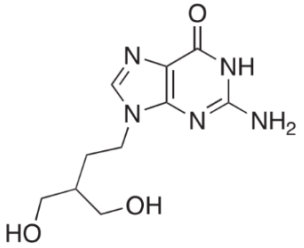
Gordon; J Bio Chem 2020.
Sheahan; Sci Transl Med 2017.
Agostini; Am Soc Micro 2018.
Yao; *CID* 2020.

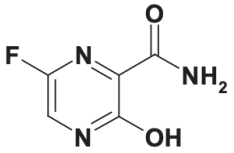
Coronaviruses and Proofreading



Ribavirin

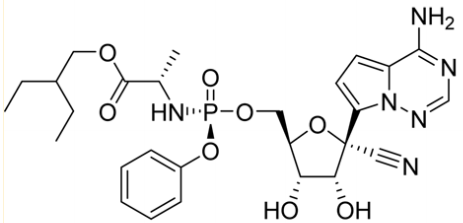


Penciclovir



Favipiravir

Removed by proofreading



Remdesivir

Maintains activity; high fitness cost

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Agostini; mBio 2018.
Smith; PLoS Pathog 2013.
Wang; Cell Res 2020.
Jordan; AAC 2018.

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.
Sheahan; Nat Comm 2020.
Sheahan; Sci Transl Med 2017.

In vivo Animal Treatment

Virus	Virologic	Clinical/Pathologic	Survival
SARS-CoV1	✓	✓	✓ (Day 1) ✗ (Day 2)
MERS	✓	✓	✗ *
Ebola	✓	✓	---

*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

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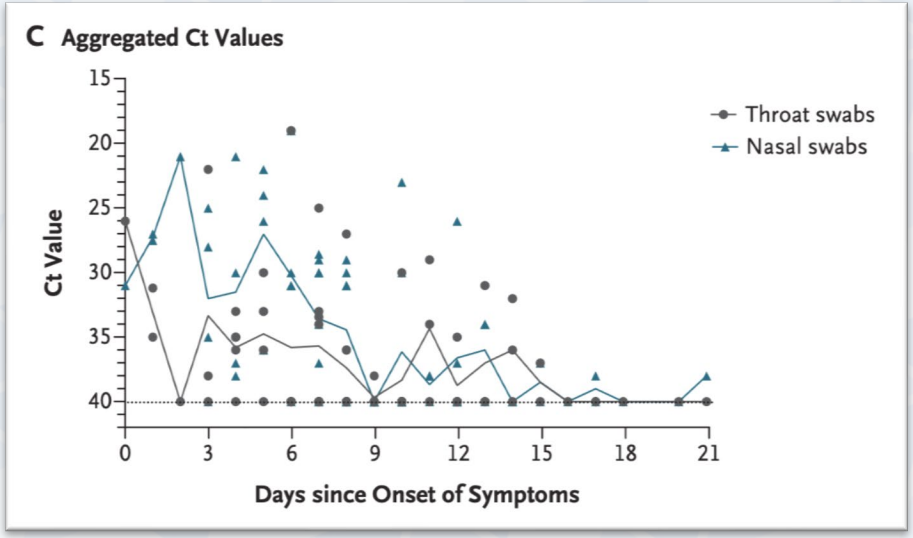
De wit E; Proc Natl Acad Sci 2020.
Sheahan; Nat Comm 2020.
Sheahan; Sci Transl Med 2017.
Warren; Nature 2016.

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



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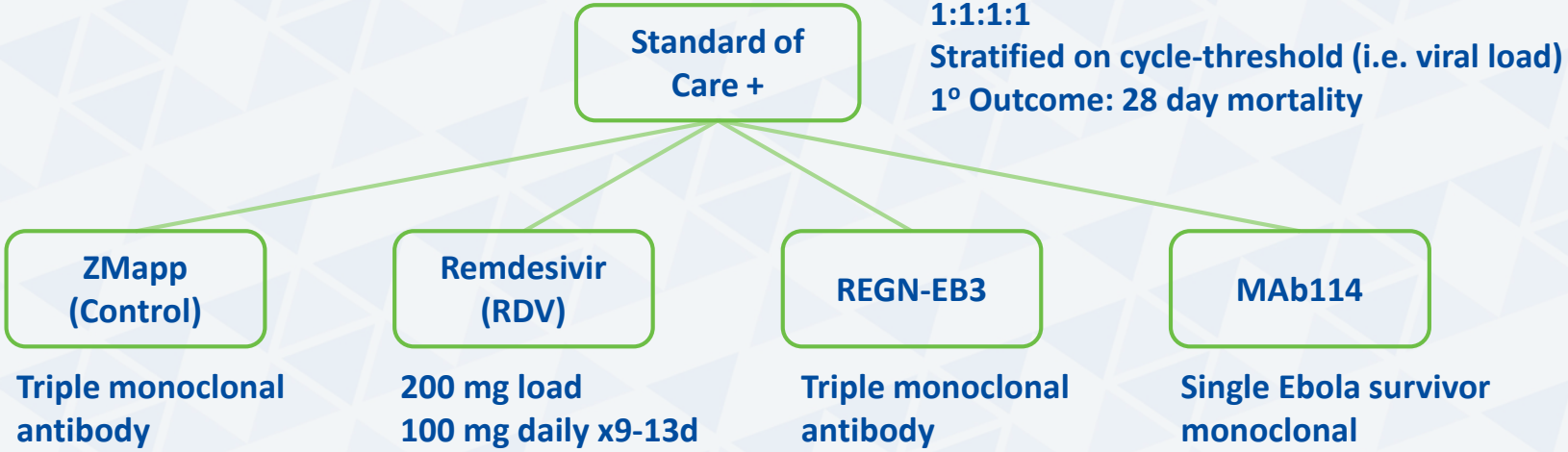
De Wit; PNAS 2020.
Zou; NEJM 2020.

Randomized, Controlled Ebola Trial



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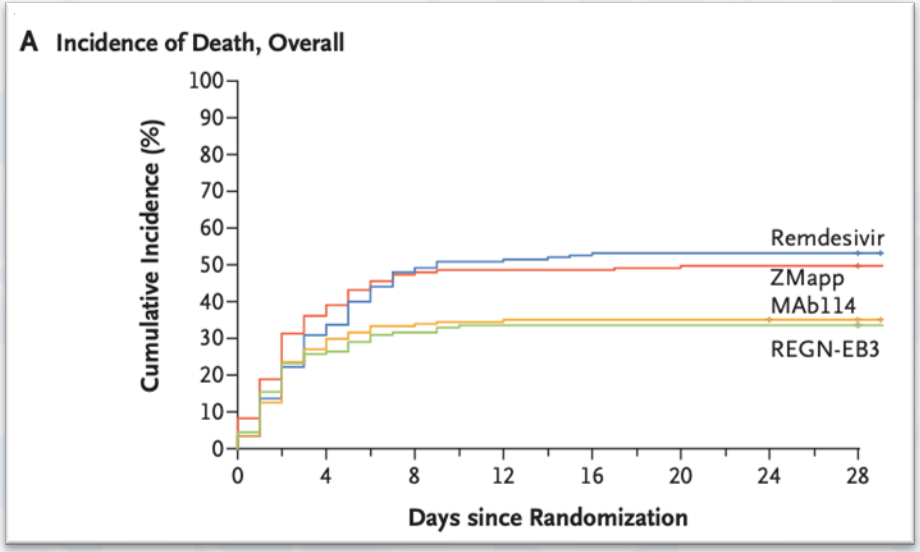
Mulangu; NEJM 2019.

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



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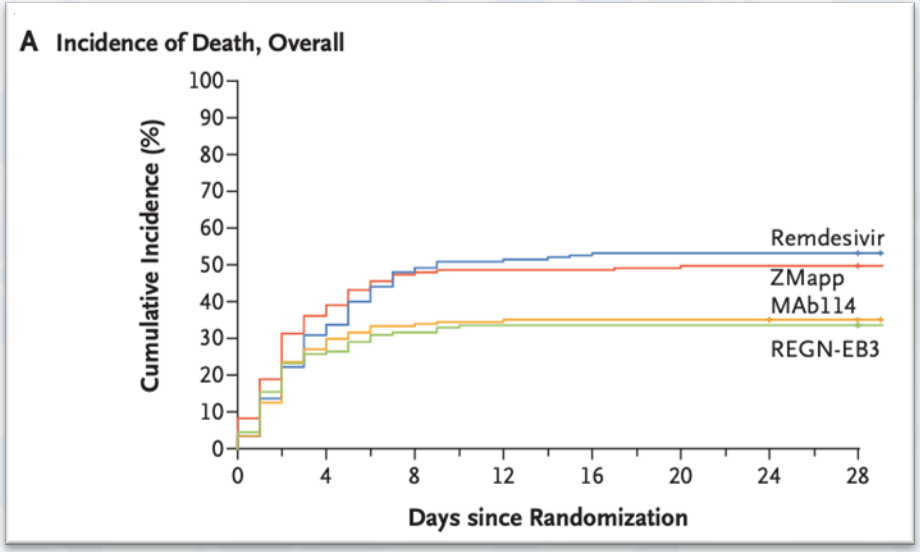
Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?



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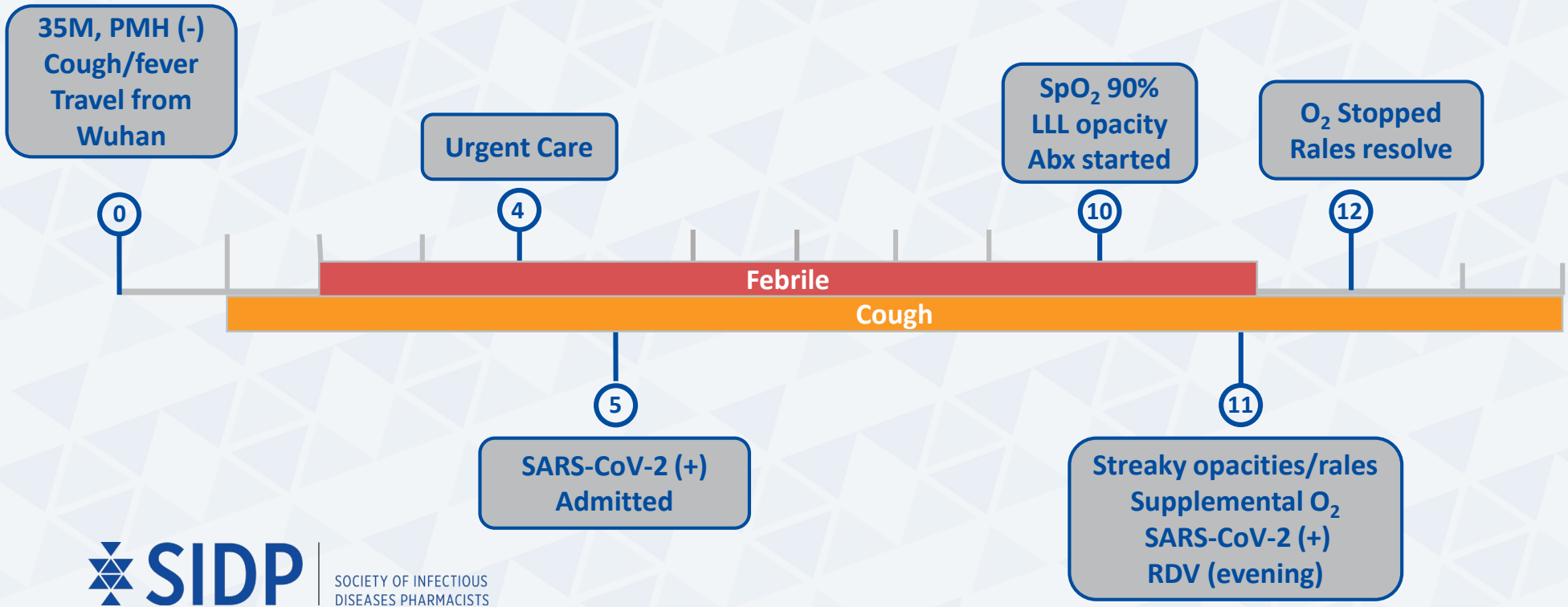
Mulangu; NEJM 2019.

First U.S. COVID-19 Case Report



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Holshue; NEJM 2020.

Remdesivir in COVID-19

- Current data insufficient to draw conclusions
- Clinical trials and compassionate use ongoing

"[...] scientists are **patiently waiting** for the final results of these ongoing trials."

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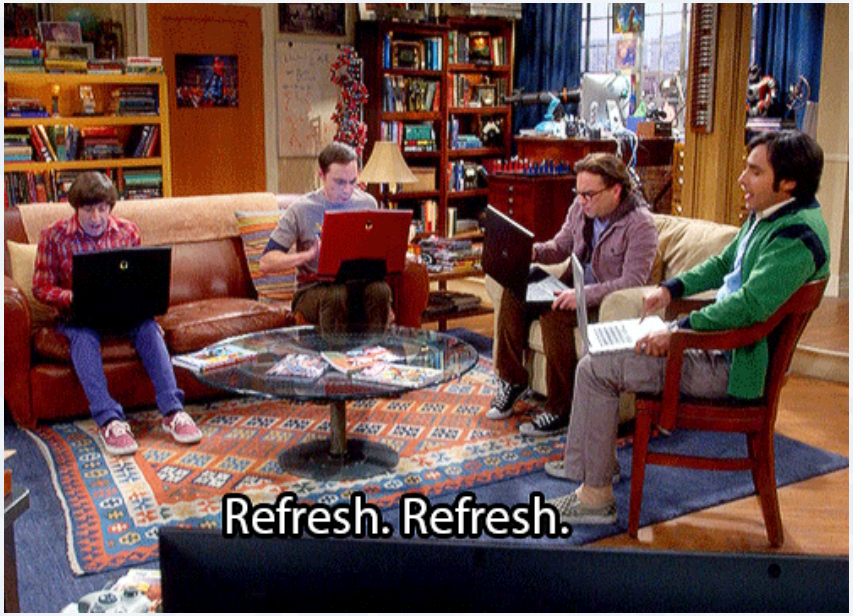
Al-tawfiq; Trav Med Inf Dis 2020.

Scientists **patiently waiting** for results



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Current Investigations

Trial	Sponsor	Population	Intervention	Renal	Completion*
Adaptive	NIAID	n = 394	RDV vs. PCB; Adaptive	eGFR < 30 mL/min	4/1/2023
Mild/Moderate	Gilead	SpO_2 ≥ 94%; n = 600	5 vs. 10 days RDV vs. SOC	CrCl < 50 mL/min	5/2020
Severe*	Gilead	SpO_2 < 94%; n = 400	5 vs. 10 days RDV vs. SOC	CrCl < 50 mL/min	5/2020
Expanded	USAMR	U.S. DoD-Affiliates; All age	RDV	eGFR < 30 mL/min	--
Mild/Mod (Ch)	CMU	SpO_2 > 94%; n = 308	RDV vs. PCB	eGFR < 30 mL/min	4/272020
Severe (Ch)	CMU	SpO_2 < 94%; n = 453	RDV vs. PCB	eGFR < 30 mL/min	5/1/2020

RDV = remdesivir; PCB = placebo; USAMR = U.S. Army Medcial R&D Command; CMU = Capital Medical University, Beijing
*All data current as of 3/16/2020, subject to change

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Source: ClinicalTrials.gov

Emergency Access

GILEAD
Creating Possible

Gilead is transitioning the provision of emergency access to remdesivir from individual compassionate use requests to expanded access programs. This approach will both accelerate access to remdesivir for severely ill patients and enable the collection of data from all participating patients. These programs are currently under rapid development in conjunction with national regulatory authorities worldwide. More details on how to participate in the expanded access programs will be forthcoming.

During this transition period, we are unable to accept new individual compassionate use requests due to an overwhelming demand over the last several days. We are focused now on processing previously approved requests and anticipate the expanded access programs will initiate in a similar expected timeframe that any new requests for compassionate use would have been processed.

Exceptions will be made only for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

Given the importance of data generation, we urge you to enroll patients in clinical trials if reasonably possible rather than pursue an emergency treatment request. Please refer to the links below for information on current clinical trials investigating the use of remdesivir in COVID-19:

- NCT04280705
- NCT04292730
- NCT04292899
- 2020-000936-23

Thank you for your understanding as we work through this transition as rapidly as possible. We are grateful for all that you are doing to serve patients in your community as we work collectively to respond to this global health crisis.

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Expanded Access Portal: https://rdvcu.gilead.com/

References

1. Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. Viruses. 2019;11(4):1-16.
2. Siegel D, Hui HC, Doerffler E, et al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. J Med Chem. 2017;60(5):1648-1661.
3. "Covid-19 Drug Interactions." University of Liverpool. http://covid19-druginteractions.org/. Accessed 3/17/2020.
4. Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019;169:104541.
5. Lo MK, Jordan R, Arvey A, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep. 2017;7(43395):1-7.
6. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396)1-10.
7. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem. 2020;1-14.
8. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 2018;9(2):1-15.
9. Yao X, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infec Dis. 2020;accepted manuscript. DOI:10.1093/cid/ciaa237.
10. Smith EC, Blanc H, Surdel MC, Vignuzzi M, Denison MR. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. PLoS Pathog. 2013;9(8):e1003565.
11. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269-271.

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References

12. Jordan PC, Stevens SK, Deval J. Nucleosides for the treatment of respiratory RNA virus infections. Antivir Chem Chemother. 2018;26:1–19.
13. De wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA. 2020;1-6.
14. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222.
15. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 2016;531(7594):381-5.
16. Oh MD, Park WB, Choe PG, et al. Viral Load Kinetics of MERS Coronavirus Infection. N Engl J Med. 2016;375(13):1303-5.
17. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020; DOI: 10.1056/NEJMc2001737.
18. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019;381(24):2293-2303.
19. Holshue ML, Debolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929-936.
20. Al-tawfiq JA, Al-homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis. 2020;101615.
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. Pearls:1)~72 hrs if approved 2)Many steps but doable 3)Model of #interprofessional ID/IDPharm aloha. We are all in." 3/16/20:20:16. Tweet.

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Questions

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