SARS-CoV-2 Clearance in the Brain and Lungs of K18-hACE2 Mice after Intranasal Liposomal Remdesivir

Frédéric Frézard

Full professor
Universidade Federal de Minas Gerais
Belo Horizonte-MG, Brazil
frezard@icb.ufmg.br

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

COVID-19 CORONAVIRUS PANDEMIC

Last updated: April 13, 2024, 01:00 GMT

Weekly Trends - Graphs - Countries - News

Coronavirus Cases:

704,753,890

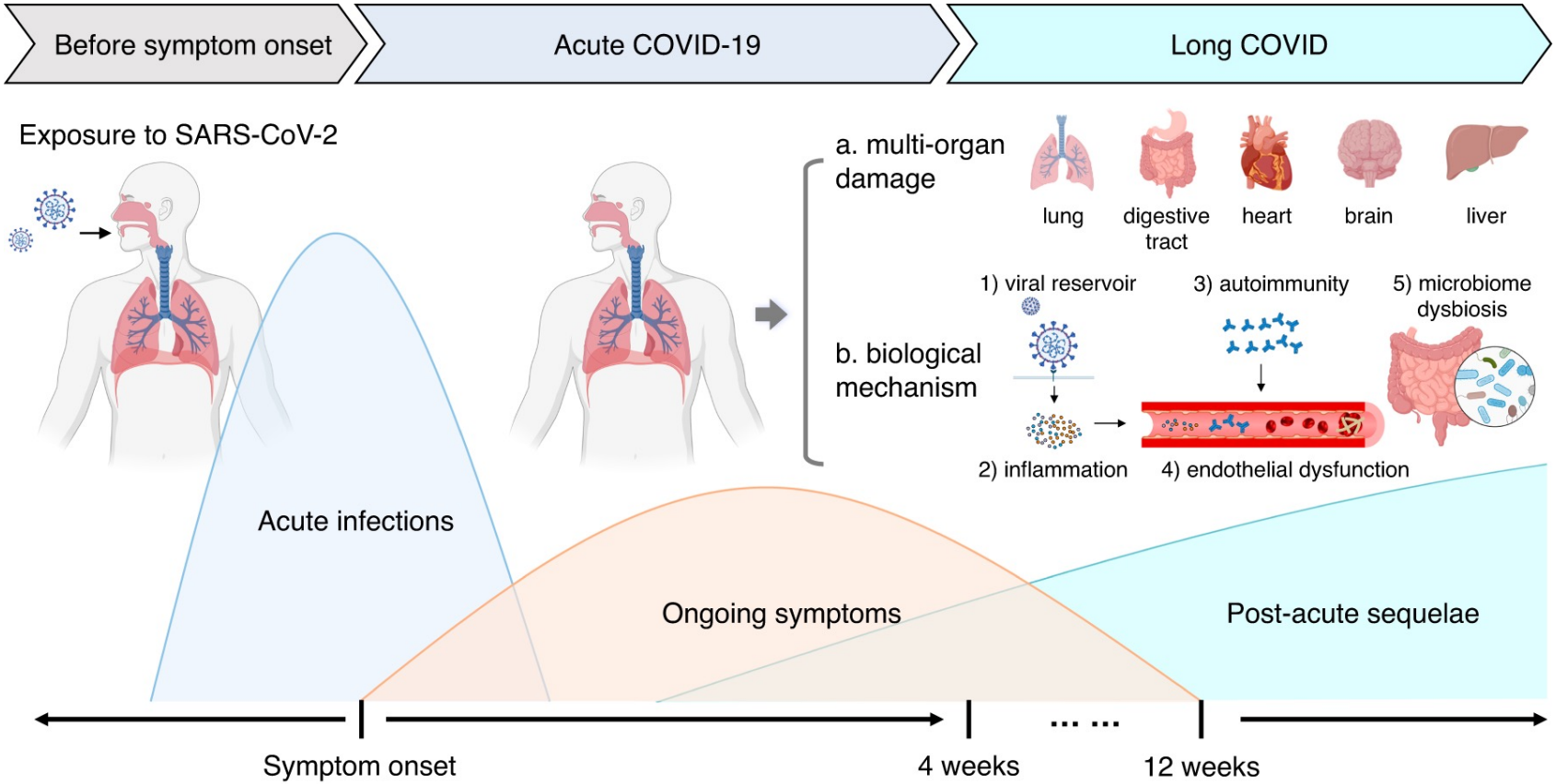
view by country

Deaths:

7,010,681

Recovered:

675,619,811



Zhou et al. Sig Transduct Target Ther 8, 416 (2023). doi: 10.1038/s41392-023-01640-z

Neurological complications caused by SARS-CoV-2

- Encephalopathy: meningitis/encephalitis, **headache**, **dizziness**
- **Neurodegenerative diseases**

  Parkinson's disease, multiple sclerosis, and Alzheimer's disease
- Delirium
- **Brain fog symptoms**

  Cognitive decline, sleep disturbances, anxiety, nutritional and mental deficiencies

Long COVID

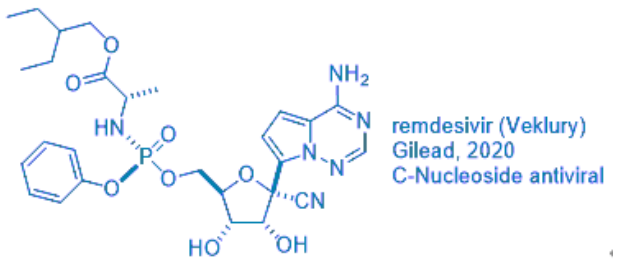
Pang et al. Clin Microbiol Rev 2024;37(4):e0013124. doi: 10.1128/cmr.00131-24.
Rahmaty et al. Med Virol. 2025;97(6):e70429. doi: 10.1002/jmv.70429.

Antiviral medications for COVID-19

COVID-19 Treatment	Who (Among people who are at high risk of getting sick)	When	How
Nirmatrelvir with Ritonavir (Paxlovid) Antiviral	Adults; children ages 12 years and older	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)
Veklury (remdesivir) Antiviral	Adults and children	Start as soon as possible; must begin within 7 days of when symptoms start	Intravenous (IV) infusions at a healthcare facility for 3 consecutive days
Molnupiravir (Lagevrio) Antiviral	Adults	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)

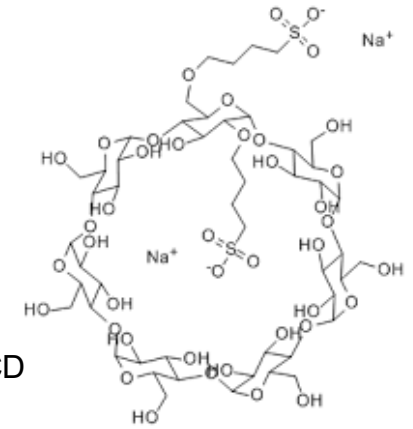
https://www.cdc.gov/covid/treatment/index.html

Veklury®: injectable Remdesivir/SBE-β-CD Complex



remdesivir (Veklury)
Gilead, 2020
C-Nucleoside antiviral

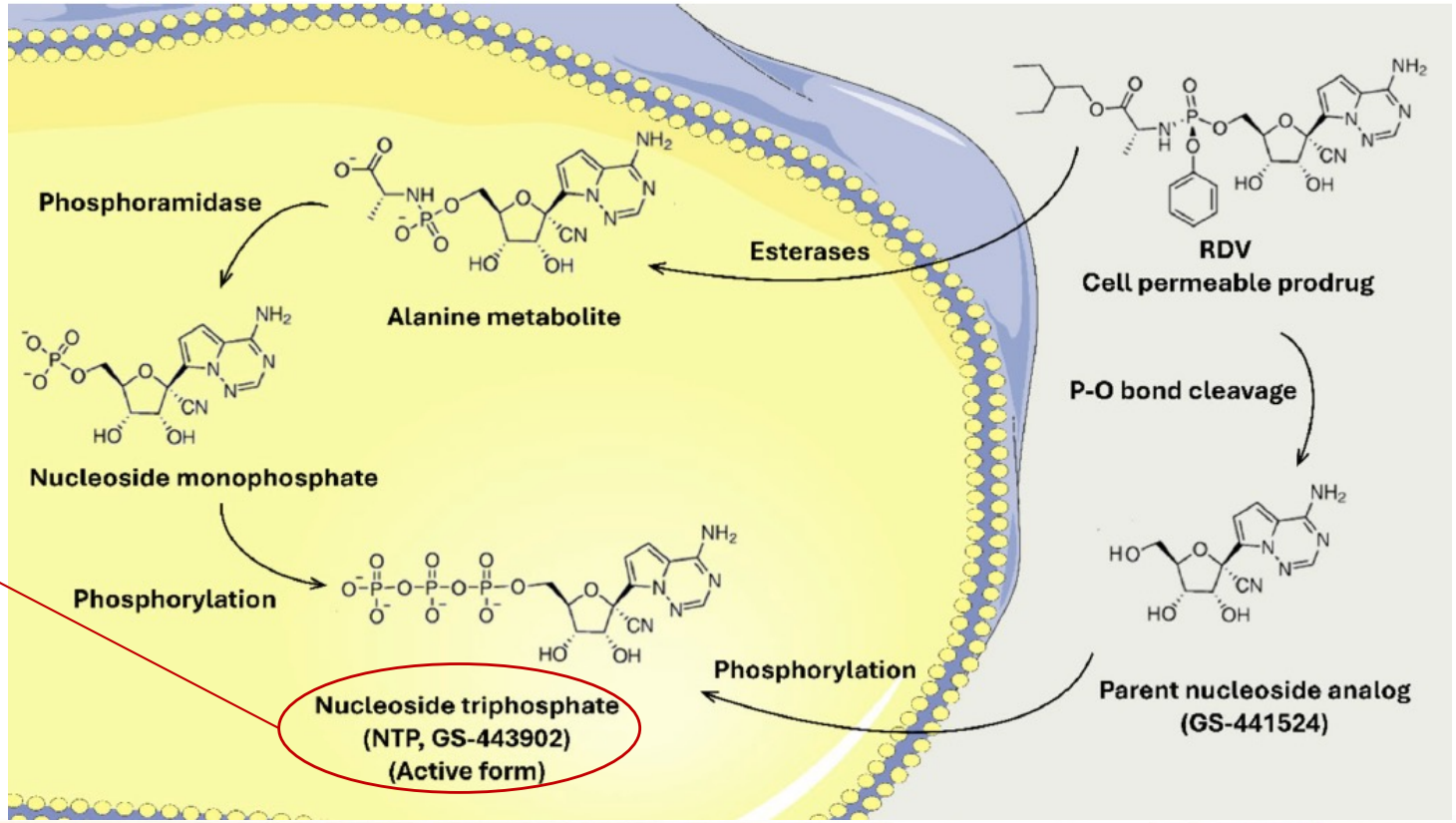
+



SBE-β-CD

Remdesivir (RDV): nucleotide analog prodrug

Inhibits RNA-dependent RNA Polymerase and virus replication



Taha et al. (2025). Drug Deliv. and Transl. Res. doi: 10.1007/s13346-025-01843-7

Veklury®/Remdesivir (RDV): Challenges and Solutions

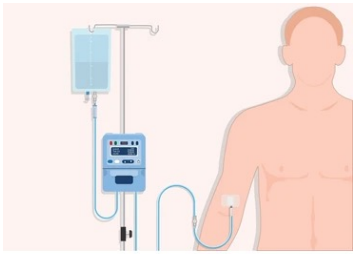
Challenges

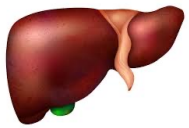
Intravenous (IV) Administration + **Vehicle-Induced Toxicity** + **Poor Lung and Brain Accumulation**

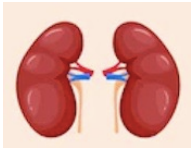
Require IV infusion because of extensive hepatic metabolism

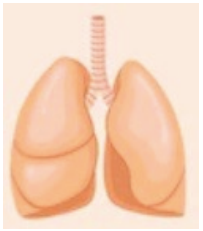
SBE-CD induces hepatic and renal toxicity at high doses

Rapid metabolism in plasma and liver leads to limited distribution in the lungs and brain









Solutions

Liposomal RDV Formulation

and Intranasal Administration

for effective drug delivery to the lungs and brain

Adapted from Taha et al. (2025). Drug Deliv. and Transl. Res. doi: 10.1007/s13346-025-01843-7

Preparation and characterization of liposomal RDV formulation (LRDV)

Vesicle formation by ethanol injection method → **Vesicle size calibration** → **Ethanol removal**

Ethanolic solution soy phosphatidylcholine + remdesivir —*injection*→ Isotonic phosphate buffer saline

Extrusion 100-nm polycarb. membranes

Dialysis

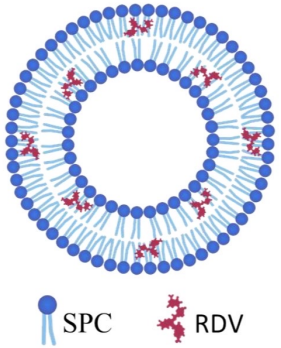


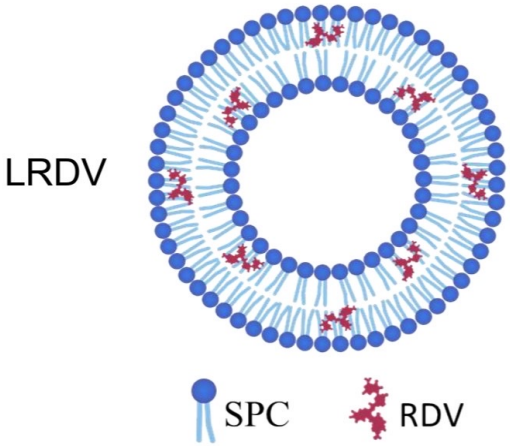
Table 1

Characteristics of conventional and PEGylated liposomal RDV formulations: particle size distribution, polydispersity index, zeta potential, and drug encapsulation efficiency.

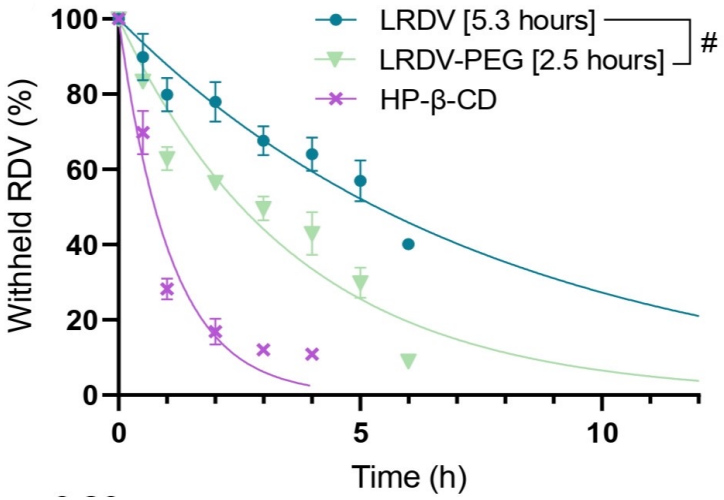
Formulation	[a]Size (nm) ± SD	[a]PDI ± SD	[a]Potential ζ (mV) ± SD	Final RDV concentration (mg/mL) ± SD	[a]EE(%) ± SD	Encapsulated drug/lipid ratio (m/m)
LRDV	118.4 ± 3.2	0.047 ± 0.024	−2.14 ± 0.18	5.4 ± 0.4 (n = 5)	59.3 ± 4.4 (*n* = 5)	0.0610
LRDV-PEG	110.1 ± 1.8	0.026 ± 0.005	−8.97 ± 0.05	1.55 ± 0.21 (n = 2)	57.2 ± 7.2 (*n* = 2)	0.0543
[b]LEmp	102.7 ± 1.7	0.056 ± 0.036	−3.55 ± 0.07		–	–
[b]LEmp-PEG	104.2 ± 2.1	0.098 ± 0.016	−2.55 ± 0.09		–	–

Mendes et al. J. Cont. Release 379 (2025) 558.

Drug release kinetics in biomimetic conditions



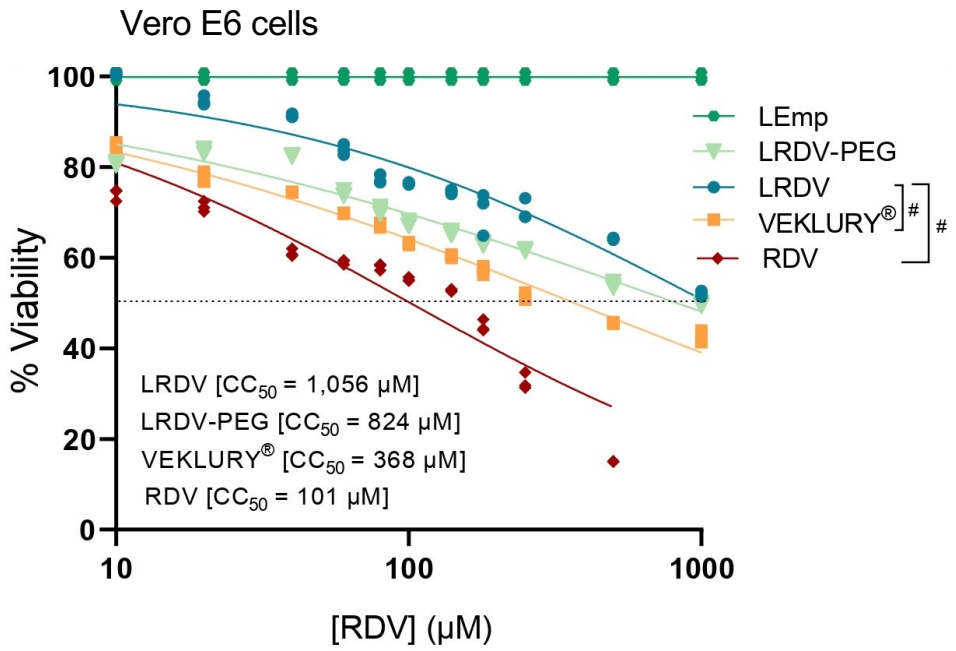
Dilution and dialysis at 37℃ against HP-βCD-containing PBS

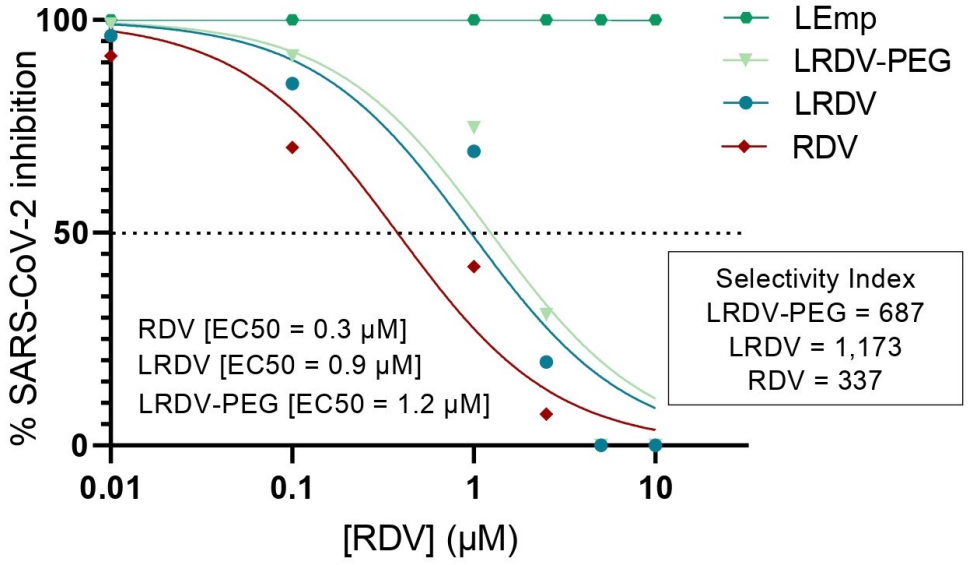


LRDV > LRDV-PEG > HP-βCD–RDV

Mendes et al. J. Cont. Release 379 (2025) 558.

In vitro cytotoxicity and antiviral activity of liposomal RDV

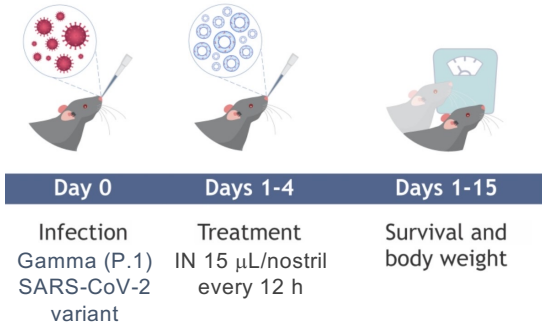


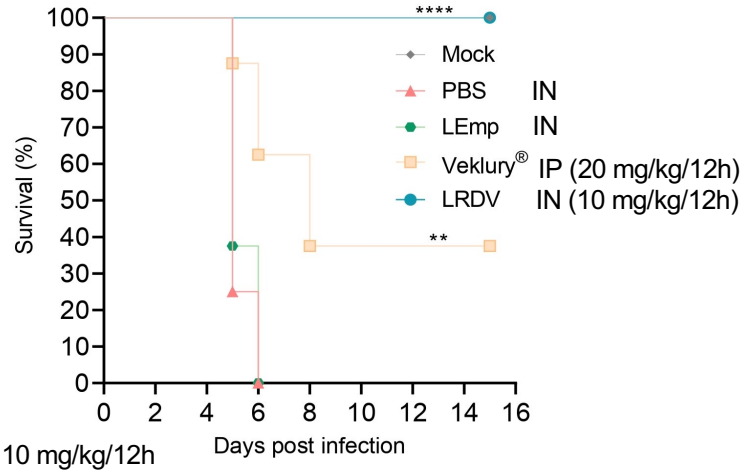


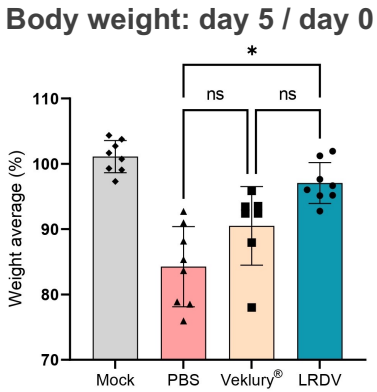
LRDV > LRDV-PEG > Veklury® > RDV

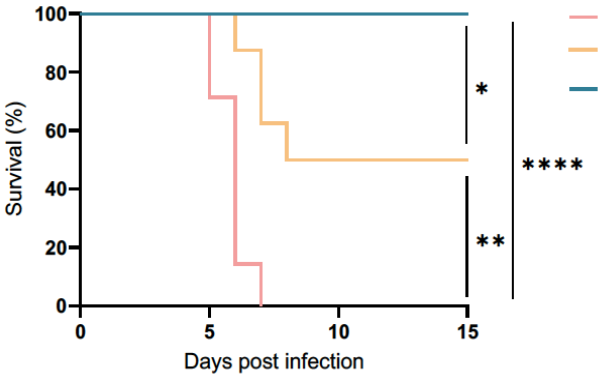
Mendes et al. J. Cont. Release 379 (2025) 558.

Survival of K18-hACE2 mice infected with SARS-CoV-2 after intranasal treatment with liposomal RDV







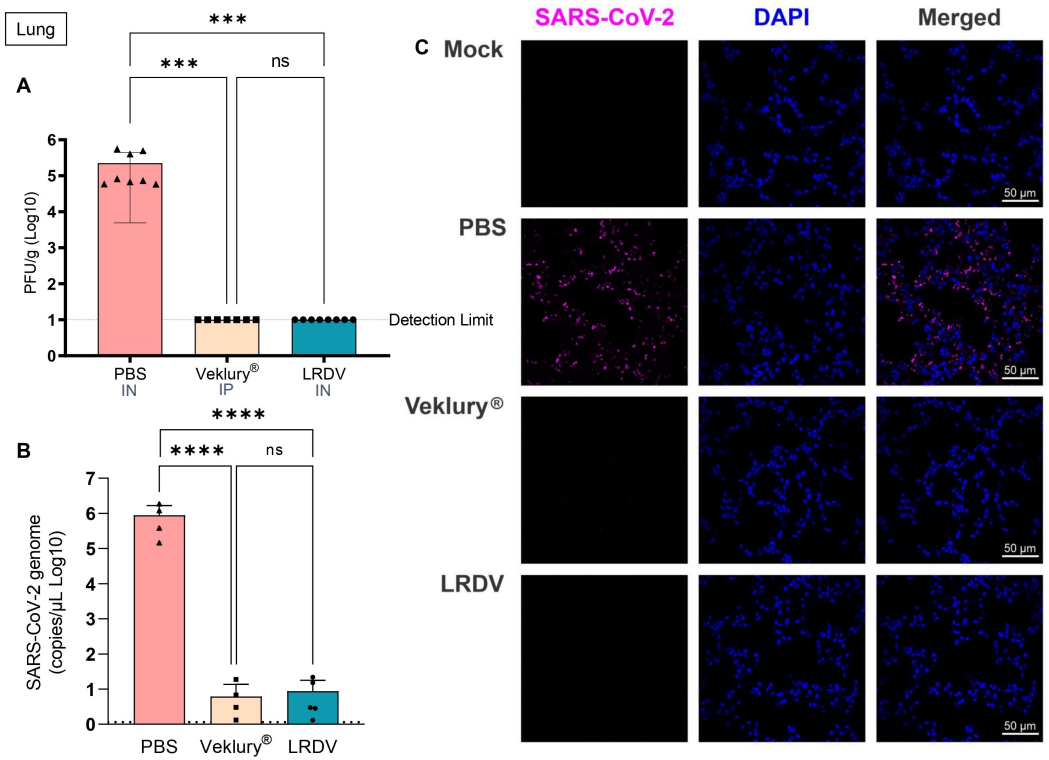


100% animal survival in LRDV group!

Liposomal carrier > Cyclodextrin carrier

Mendes et al. J. Cont. Release 379 (2025) 558.

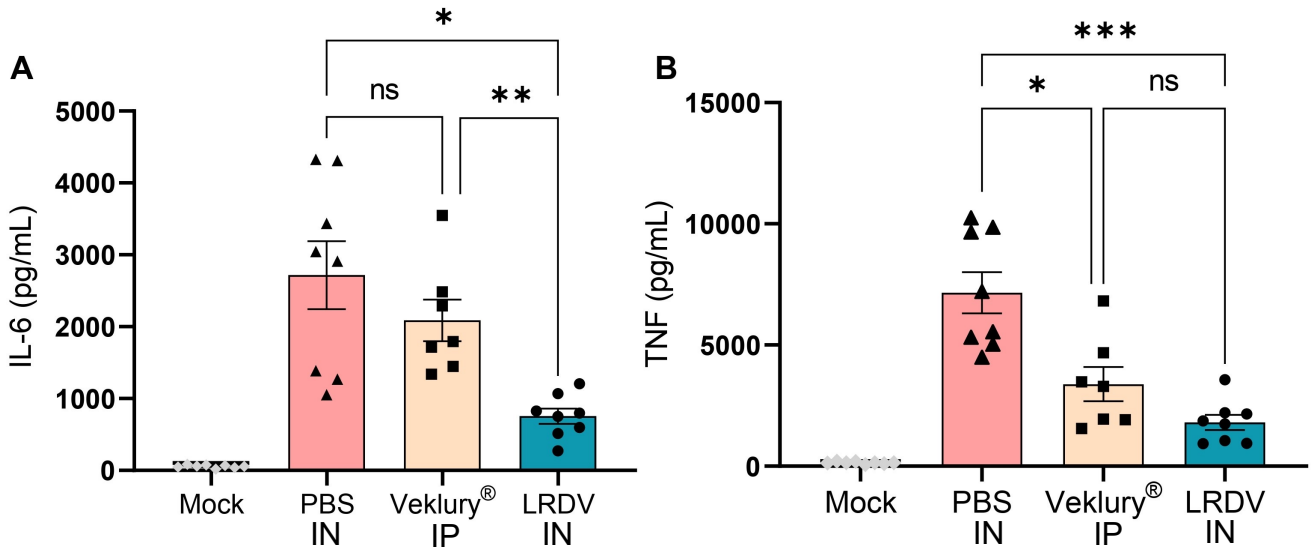
Viral load in the lung of K18-hACE2 mice infected with SARS-CoV-2 after intranasal treatment with liposomal RDV



Intranasal LRDV is as effective as parenteral Veklury® in eliminating virus in the lungs

Mendes et al. J. Cont. Release 379 (2025) 558.

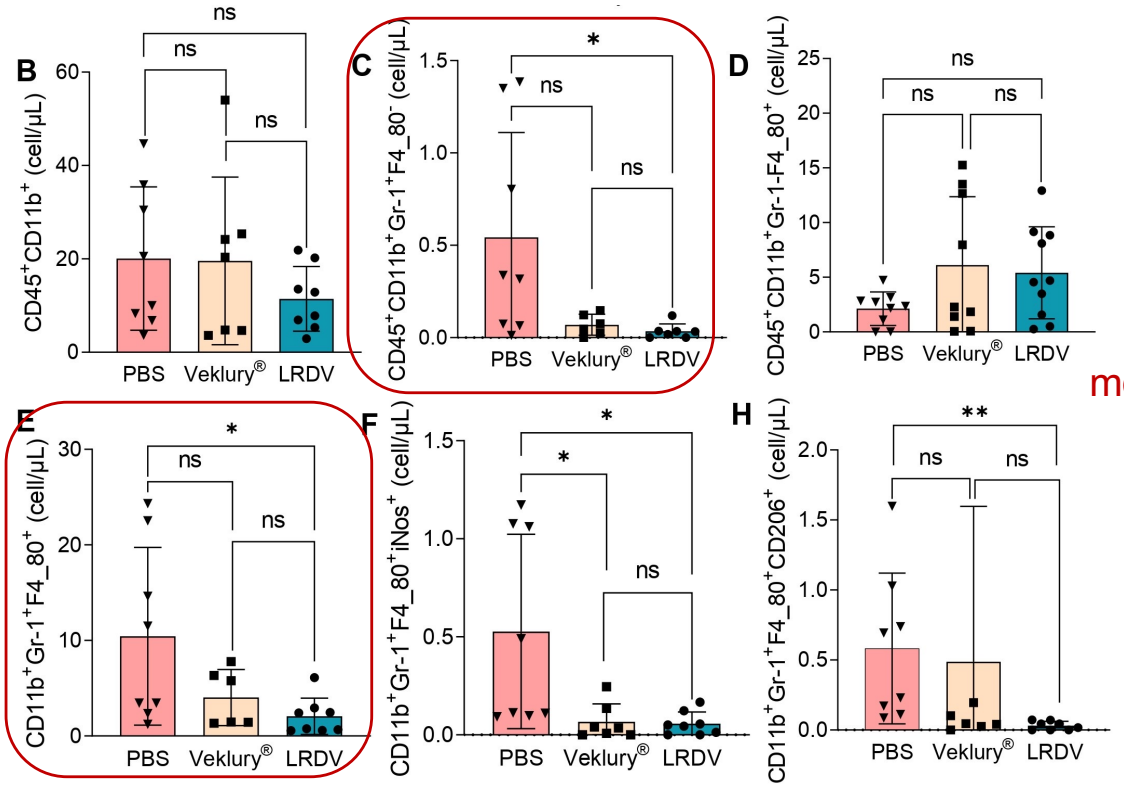
Proinflammatory cytokines in the lung of SARS-CoV-2-infected K18-hACE2 mice after intranasal treatment with liposomal RDV



Intranasal LRDV inhibits IL-6 and TNF production in the lungs more effectively than parenteral Veklury®

Mendes et al. J. Cont. Release 379 (2025) 558.

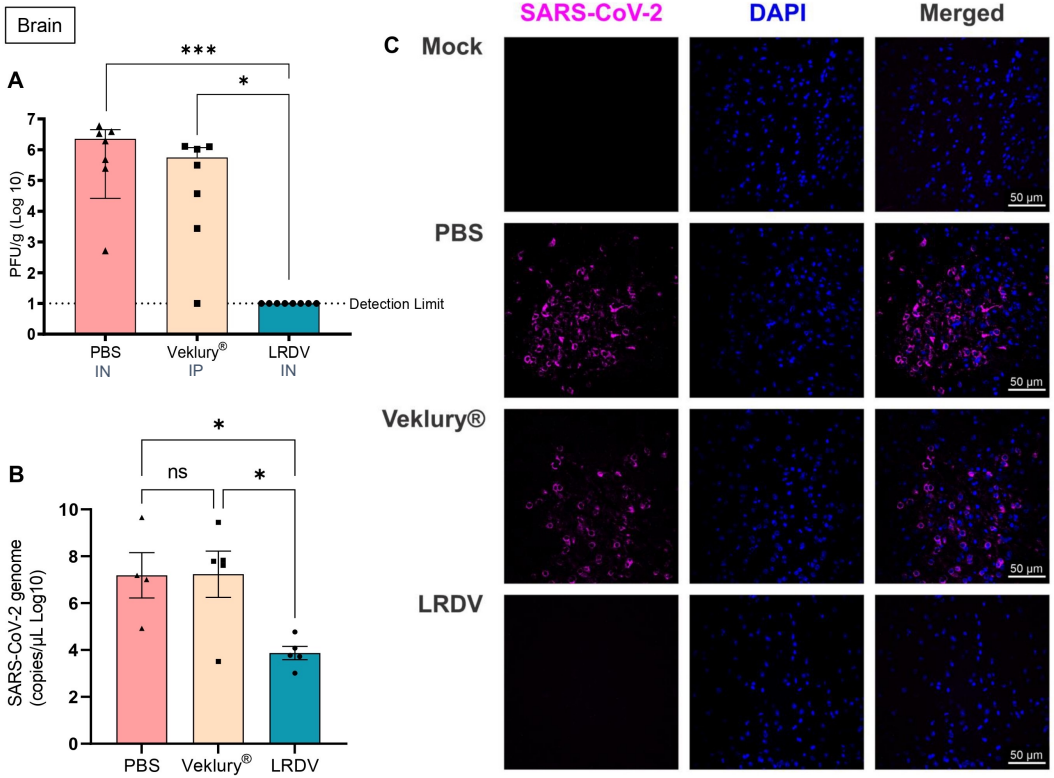
Myeloid cells in lungs of SARS-CoV-2-infected K18 mice



Intranasal LRDV inhibits the migration of neutrophils and monocytes more effectively than parenteral Veklury®

Mendes et al. J. Cont. Release 379 (2025) 558.

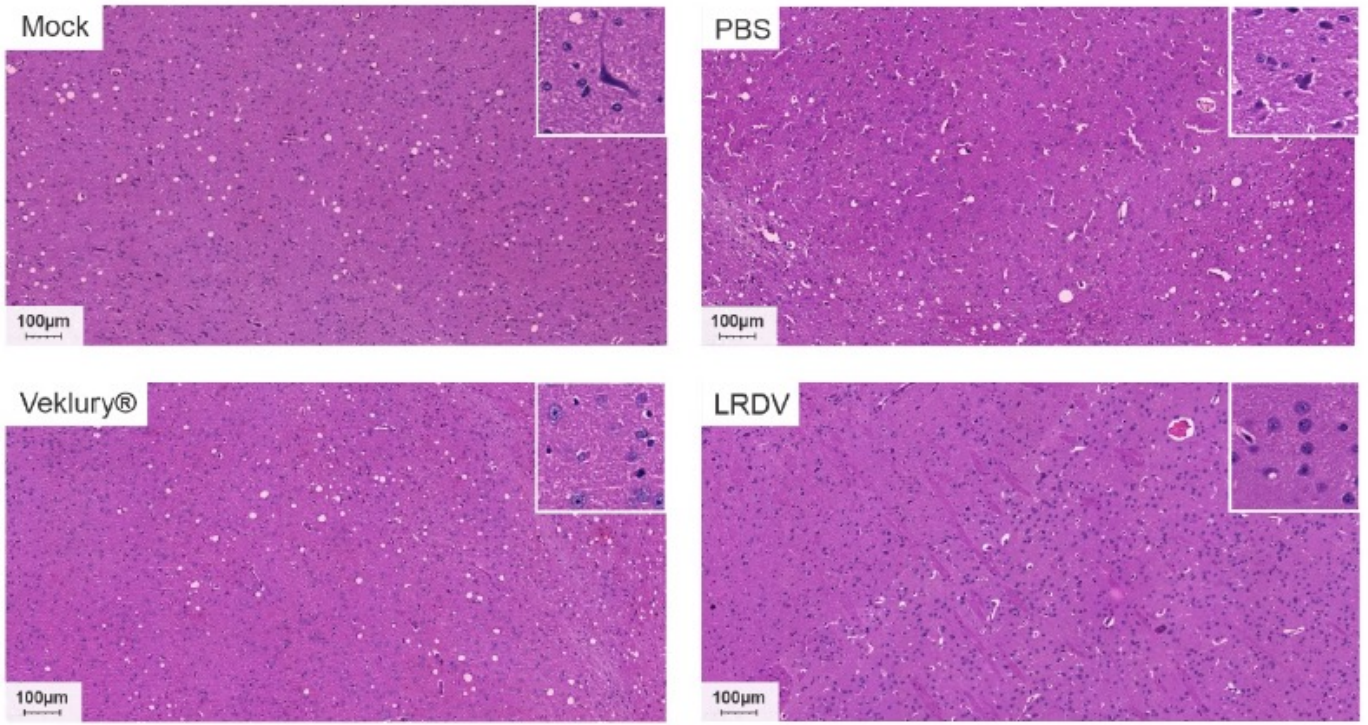
Viral load in the brain of SARS-CoV-2-infected K18-hACE2 mice after treatment with liposomal RDV



Intranasal LRDV reduced viral load in the brain contrary to parenteral Veklury®

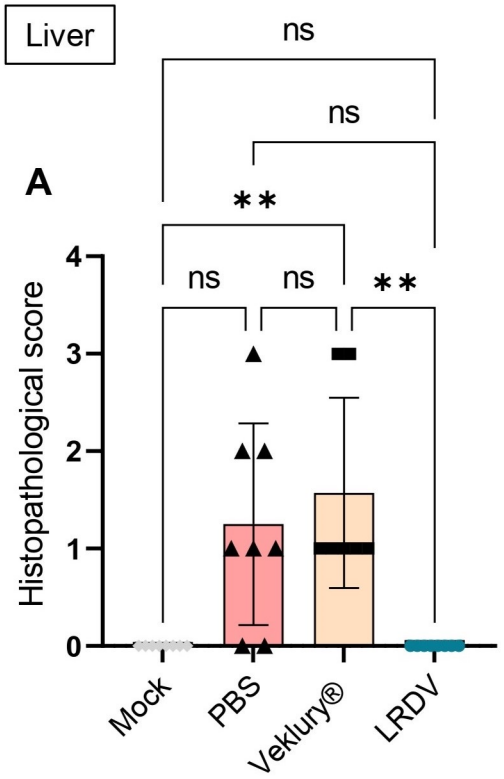
Mendes et al. J. Cont. Release 379 (2025) 558.

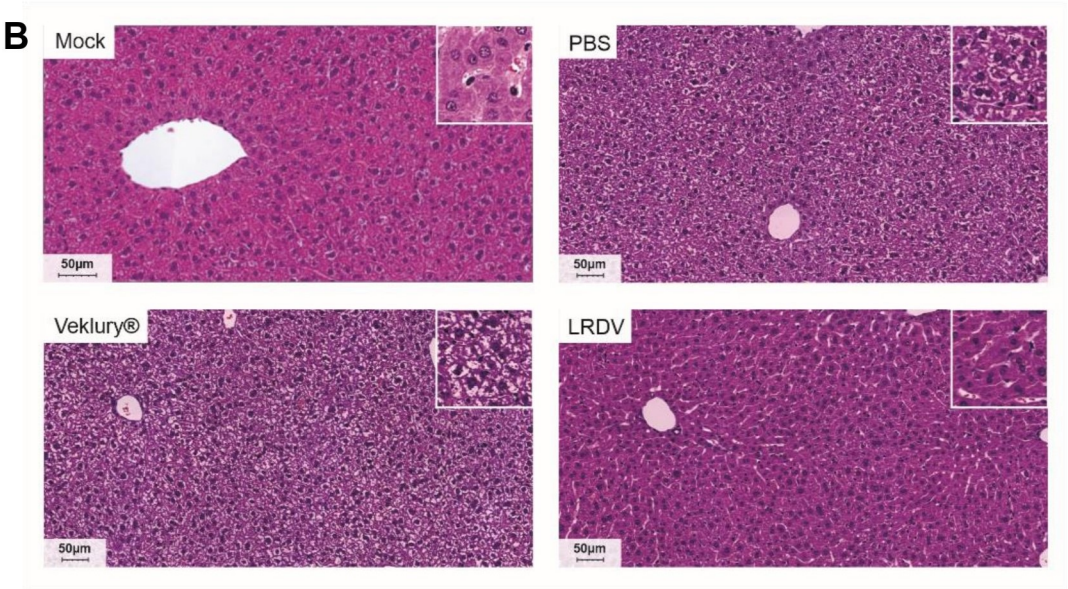
Histology of the brain of SARS-CoV-2-infected K18-hACE2 mice after intranasal treatment with liposomal RDV



Mendes et al. J. Cont. Release 379 (2025) 558.

Histopathology evaluation of the liver of SARS-CoV-2-infected K18-hACE2 mice after intransal treatment with liposomal RDV

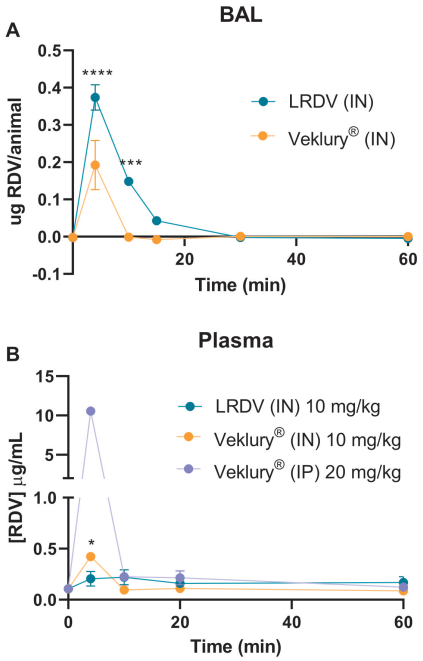


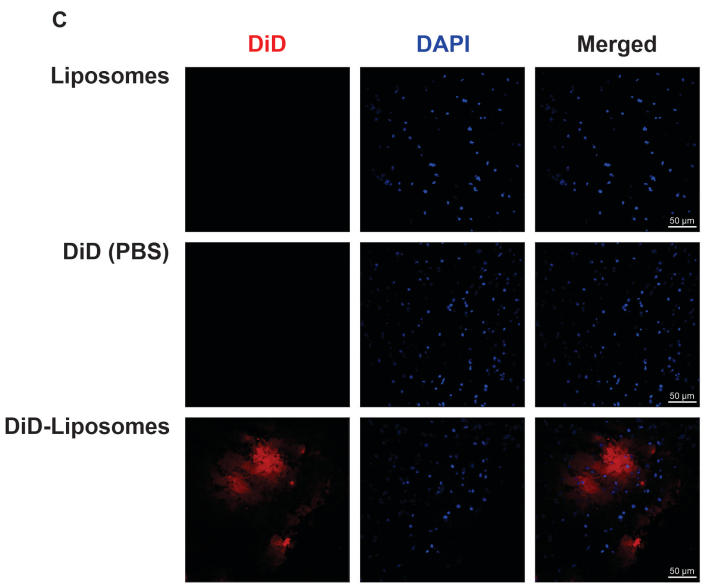


No sign of hepatotoxicity of intranasal LRDV
Systemic antiviral action of IN LRDV is suggested

Mendes et al. J. Cont. Release 379 (2025) 558.

Pharmacokinetics of RDV in mice and liposome distribution to the brain





Mendes et al. J. Cont. Release 379 (2025) 558.

Hypothesis Mode of action of LRDV

Local action of RDV (short Half-life) → Transformation into GS441524 active metabolite (long Half-life) → Absorption of GS441524 to the circulation and systemic action

Conclusions

- First report of effective delivery of RDV simultaneously to the brain and lungs with a successful therapeutic outcome in COVID-19 mouse model with no sign of toxicity.

- Intranasal liposomal RDV holds promise for early therapy of COVID-19 in non-hospitalized patients and prevention of Long COVID

Acknowledgements

Universidade Federal de Minas Gerais

Lab. Biophysics of Nanostructured Systems

Dr. **Sabrina Mendes**
Dr. Lays Cordeiro Guimarães
Dr. Pedro Augusto Carvalho Costa
MSc. Natália Jordana Alves da Silva
MSc. Gabriel Silva Alves Pessim Pereira
MSc. Clara Couto Fernandez
Prof. Robson Augusto Souza dos Santos
Prof. Pedro Pires Goulart Guimarães

Dept. Biochemistry & Immunology

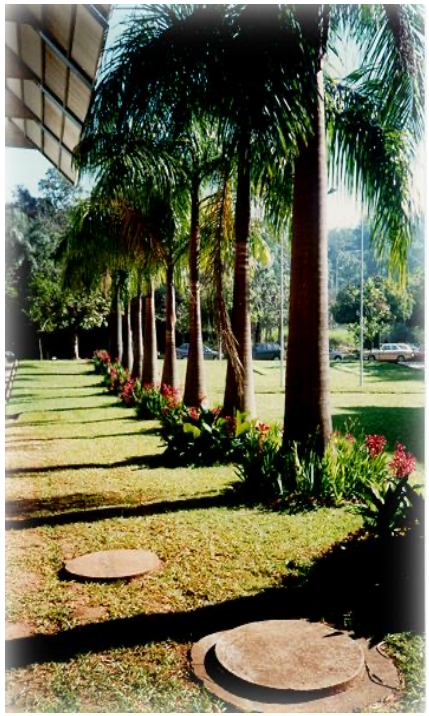
Prof. Mauro Martins Teixeira
Dr. Leonardo Camilo de Oliveira

Dept. Morphology

Profa. Vivian Vasconcelos Costa

State University de Minas Gerais (UEMG)

Ptofa. Maria Marta Figueiredo



- ✓ National Institute of Science and Technology in Dengue and Host-Microorganism Interaction (INCT em Dengue)
- ✓ National Institute of Science and Technology in Nanobiopharmaceutics (INCT NanoBiofar)
- ✓ NanoLung Network of Minas Gerais
- ✓ CT in Advanced and Innovative Therapies, UFMG