Lessons learned from the mechanism of action and pharmacokinetic-pharmacodynamic relationships for antiviral medicines evaluated during the COVID-19 pandemic.

Andrew Owen, Ph.D. FRSB. FBPhS. FLSW.
Centre of Excellence in Long-acting Therapeutics (CELT)
University of Liverpool, UK

@_AndrewOwen_

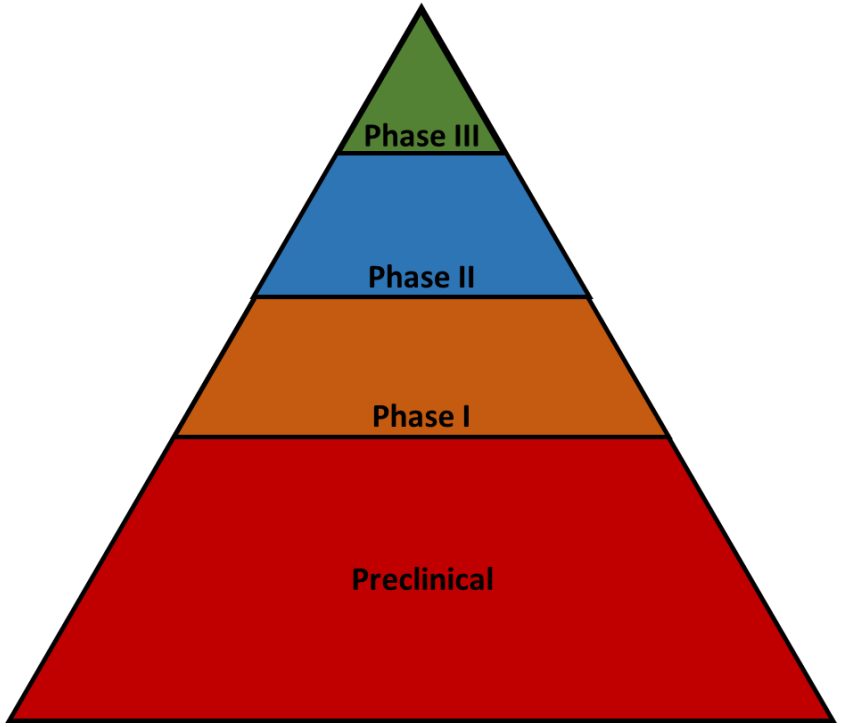
andrew-owen-44200026

Disclosures

- Director and Chief Scientific Officer for Tandem Nano Ltd.
- Co-inventor of patents relating to drug delivery for communicable and non-communicable diseases.
- Grant funding from ViiV Healthcare and Gilead unrelated to the presented work.
- Consultancy and/or speaker fees from Gilead, ViiV Healthcare and Assembly Biosciences unrelated to the presented work.

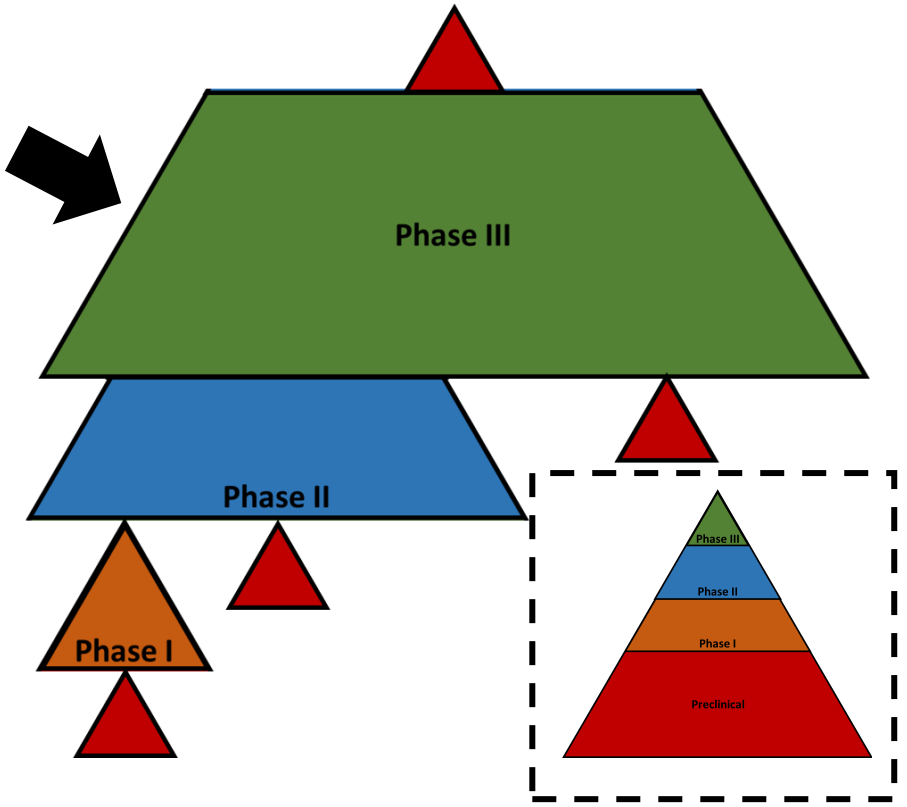
What did we (re)learn in the first 12 months?

What I've been taught for the past 25 years



What the first 12 months of the pandemic felt like

Hydroxychloroquine
Lopinavir / ritonavir
Sofosbuvir
Ivermectin
Etc.



Nirmatrelvir / ritonavir
Molnupiravir
Sotrovimab

What did we (re)learn in the first 12 months?

- The mechanism of action must be demonstrated, plausible and be tested in RCTs.
- In vitro activity is highly relevant but needs to be considered in the context of the pharmacokinetics (PK-PD; exposure-response).
- Repurposed drugs can be highly valuable but only when appropriately validated and tested.
- Non-randomised clinical evidence is unreliable (badly conducted RCTs are too).

The mechanism of action must be demonstrated, plausible and tested in RCTs.

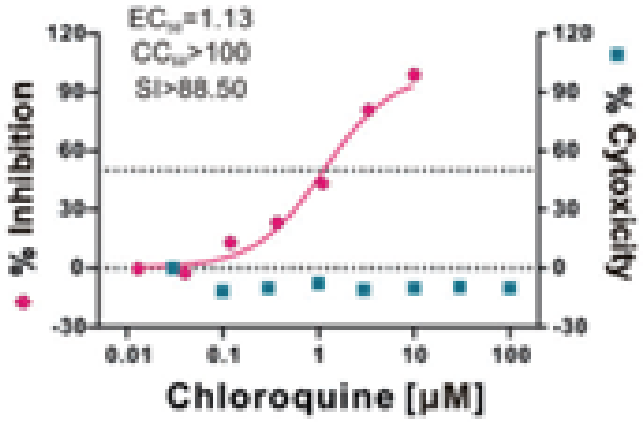
Cell Research — February 2020

www.nature.com/cr
www.cell-research.com

LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0



"Chloroquine is known to block virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV."

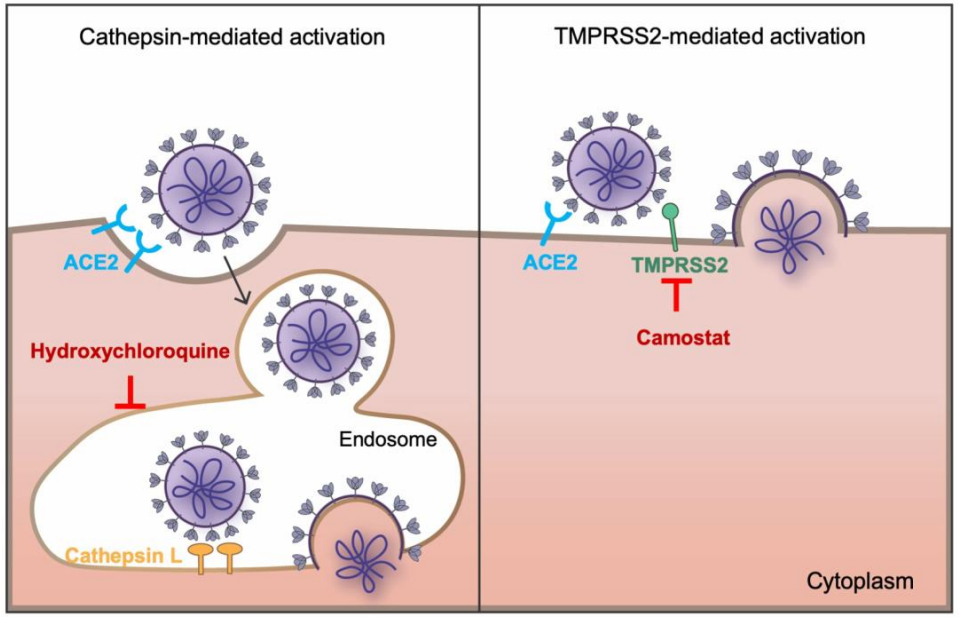
PLOS PATHOGENS — January 2021

RESEARCH ARTICLE

Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2

Tianling Ou*, Huihui Mou, Lizhou Zhang, Amrita Ojha, Hyeryun Choe, Michael Farzan*

Department of Immunology and Microbiology, The Scripps Research Institute, Jupiter, Florida, United States



- Phase III evaluation of 4-aminoquinolines was underway prior to emergence of prerequisite knowledge about the mechanism of action.

In vitro activity is highly relevant but needs to be considered in the context of the pharmacokinetics (PK-PD; exposure-response).

Preprinted April 2020

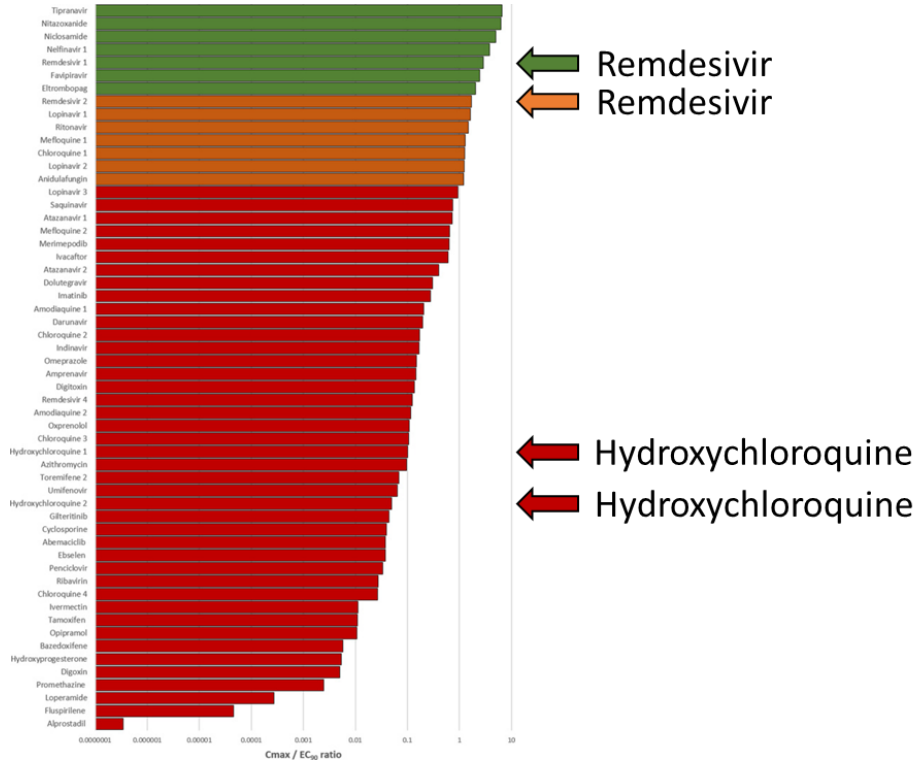
ARTICL

Check for updates

Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics

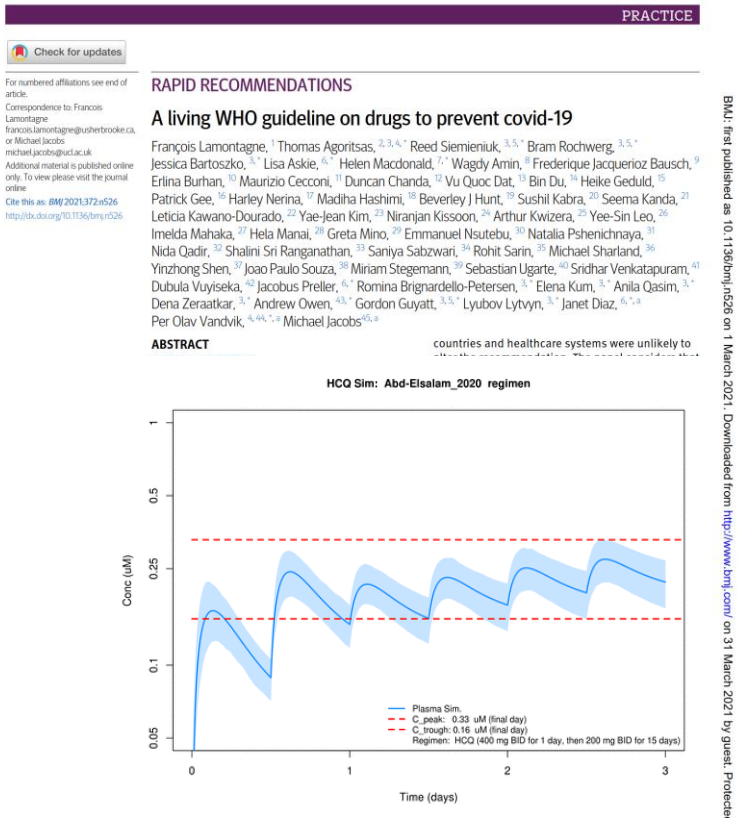
Usman Arshad[1], Henry Pertinez[1], Helen Box[1], Lee Tatham[1], Rajith K. R. Rajoli[1], Paul Curley[1], Megan Neary[1], Joanne Sharp[1], Neill J. Liptrott[1], Anthony Valentijn[1], Christopher David[1], Steve P. Rannard[2], Paul M. O'Neill[2], Ghaith Aljayyoussi[3], Shaun H. Pennington[3], Stephen A. Ward[3], Andrew Hill[1], David J. Back[1], Saye H. Khoo[1], Patrick G. Bray[4], Giancarlo A. Biagini[3] and Andrew Owen[1,*]

There is a rapidly expanding literature on the *in vitro* antiviral activity of drugs that may be repurposed for therapy or chemoprophylaxis against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). However, this has not been accompanied by a comprehensive evaluation of the target plasma and lung concentrations of these drugs following approved dosing in humans. Accordingly, concentration 90% (EC_{90}) values recalculated from *in vitro* anti-SARS-CoV-2 activity data was expressed as a ratio to the achievable maximum plasma concentration (C_{max}) at an approved dose in humans (C_{max}/EC_{90} ratio). Only 14 of the 56 analyzed drugs achieved a C_{max}/EC_{90} ratio above 1. A more in-depth assessment demonstrated that only nitazoxanide, nelfinavir, tipranavir (ritonavir-boosted), and sulfadoxine achieved plasma concentrations above their reported anti-SARS-CoV-2 activity across their entire approved dosing interval. An unbound lung to plasma tissue partition coefficient (K_pU_{lung}) was also simulated to derive a lung C_{max}/half-maximal effective concentration (EC_{50}) as a better indicator of potential human efficacy. Hydroxychloroquine, chloroquine, mefloquine, atazanavir (ritonavir-boosted), tipranavir (ritonavir-boosted), ivermectin, azithromycin, and lopinavir (ritonavir-boosted) were all predicted to achieve lung concentrations over 10-fold higher than their reported EC_{50}. Nitazoxanide and sulfadoxine also exceeded their reported EC_{50} by 7.8-fold and 1.5-fold in lung, respectively. This analysis may be used to select potential candidates for further clinical testing, while deprioritizing compounds unlikely to attain target concentrations for antiviral activity. Future studies should focus on EC_{90} values and discuss findings in the context of achievable exposures in humans, especially within target compartments, such as the lungs, in order to maximize the potential for success of proposed human clinical trials.



- Sufficient data existed to conclude that hydroxychloroquine, lopinavir and other repurposed drugs would not achieve antiviral concentrations in the plasma of patients prior to initiation of clinical trials.
- While initially studied for antiviral properties, proponents of hydroxychloroquine and ivermectin continued to argue in favour of secondary mechanisms of action (e.g. immunomodulation), which were plausible but unproven.

In vitro activity is highly relevant but needs to be considered in the context of the pharmacokinetics (PK-PD; exposure-response).



PRACTICE

Check for updates

RAPID RECOMMENDATIONS

A living WHO guideline on drugs to prevent covid-19

François Lamontagne, [1] Thomas Agoritsas, [2,3,4,*] Reed Siemieniuk, [3,5,*] Bram Rochwerg, [3,5,*] Jessica Bartoszko, [3,*] Lisa Askie, [6,*] Helen Macdonald, [7,*] Wagdy Amin, [8] Frederique Jacquerioz Bausch, [9] Erlina Burhan, [10] Maurizio Cecconi, [11] Duncan Chanda, [12] Vu Quoc Dat, [13] Bin Du, [14] Heike Geduld, [15] Patrick Gee, [16] Harley Nerina, [17] Madiha Hashimi, [18] Beverley J Hunt, [19] Sushil Kabra, [20] Seema Kanda, [21] Leticia Kawano-Dourado, [22] Yae-Jean Kim, [23] Niranjan Kissoon, [24] Arthur Kwizera, [25] Yee-Sin Leo, [26] Imelda Mahaka, [27] Hela Manai, [28] Greta Mino, [29] Emmanuel Nsutebu, [30] Natalia Pshenichnaya, [31] Nida Qadir, [32] Shalini Sri Ranganathan, [33] Saniya Sabzwari, [34] Rohit Sarin, [35] Michael Sharland, [36] Yinzhong Shen, [37] Joao Paulo Souza, [38] Miriam Stegemann, [39] Sebastian Ugarte, [40] Sridhar Venkatapuram, [41] Dubula Vuyiseka, [42] Jacobus Preller, [6,*] Romina Brignardello-Petersen, [3,*] Elena Kum, [3,*] Anila Qasim, [3,*] Dena Zeraatkar, [3,*] Andrew Owen, [43,*] Gordon Guyatt, [3,5,*] Lyubov Lytvyn, [3,*] Janet Diaz, [6,*,a] Per Olav Vandvik, [4,44,*,a] Michael Jacobs [45,a]

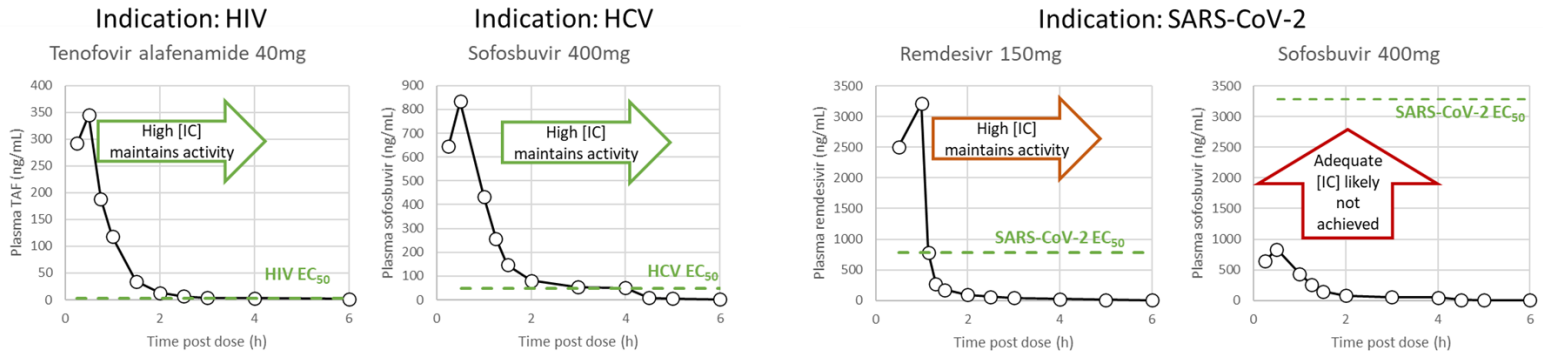
For numbered affiliations see end of article.
Correspondence to: Francois Lamontagne francois.lamontagne@usherbrooke.ca, or Michael Jacobs michael.jacobs@ucl.ac.uk

Additional material is published online only. To view please visit the journal online
Cite this as: *BMJ* 2021;372:n526
http://dx.doi.org/10.1136/bmj.n526

ABSTRACT

countries and healthcare systems were unlikely to

- ProTide technology is distinct from some other prodrug technologies because the objective is to deliver intact prodrug into the plasma compartment as a primary objective of the approach.
- *The active intracellular moiety is the same but since ProTide intracellular accumulation and residence time is higher, the apparent EC_{50}/EC_{90} (an extracellular metric!) is lower than the native nucleoside.*



- Sufficient data existed to conclude that hydroxychloroquine, lopinavir and other repurposed drugs would not achieve antiviral concentrations in the plasma of patients prior to initiation of clinical trials.

UNIVERSITY OF LIVERPOOL | CELT

Repurposed drugs can be highly valuable but only when appropriately validated and tested.

- Remdesivir was developed to treat hepatitis C virus infection and was also studied for Ebola and Marburg virus infections before being repurposed for SARS-CoV-2.
- Molnupiravir was designed as an orally administered influenza treatment and repurposed early in development as an antiviral for SARS-CoV-2.
- Nirmatrelvir was developed as an orally deliverable analogue of an intravenous prodrug originally developed for SARS-CoV (lufotrelvir; PF-07304814) and subsequently repurposed for SARS-CoV-2.
- Although development only began in December 2019, sotrovimab was identified from the blood of patients infected with SARS-CoV (not SARS-CoV-2).

Non-randomised clinical evidence is unreliable (badly conducted RCTs are too).

J Antimicrob Chemother 2023; **78**: 323–327
https://doi.org/10.1093/jac/dkac437 Advance Access publication 28 December 2022

Journal of Antimicrobial Chemotherapy

The dangers of non-randomized, observational studies: experience from the COVID-19 epidemic

Andrew Hill[1] and Manya Mirchandani[2]*

[1]*Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L7 3NY, UK;* [2]*Faculty of Medicine, Imperial College London, London SW7 2BX, UK*

*Corresponding author. E-mail: manya.6269@gmail.com

Table 1. Comparison of results from non-randomized and randomized trials of six potential treatments for COVID-19

Drug	Non-randomized study	Estimated benefits in non-randomized study	RCT	Estimated benefits in randomized trials
Ivermectin	Rajter *et al.*[8] *n*=280	Mortality: 40% lower risk RR: 0.60 (95% CI 0.37–0.96), *P*=0.03	COVID-NMA *n*=1369	Mortality: no significant difference RR: 0.77 (95% CI 0.47–1.29), *P*=0.93
Hydroxychloroquine	Arshad *et al.*[9] *n*=1611	Mortality: 49% lower risk RR: 0.51 (95% CI 0.41–0.63), *P*<0.00001	COVID-NMA *n*=8655	Mortality: no significant difference RR: 1.07 (95% CI 0.98–1.17), *P*=0.83

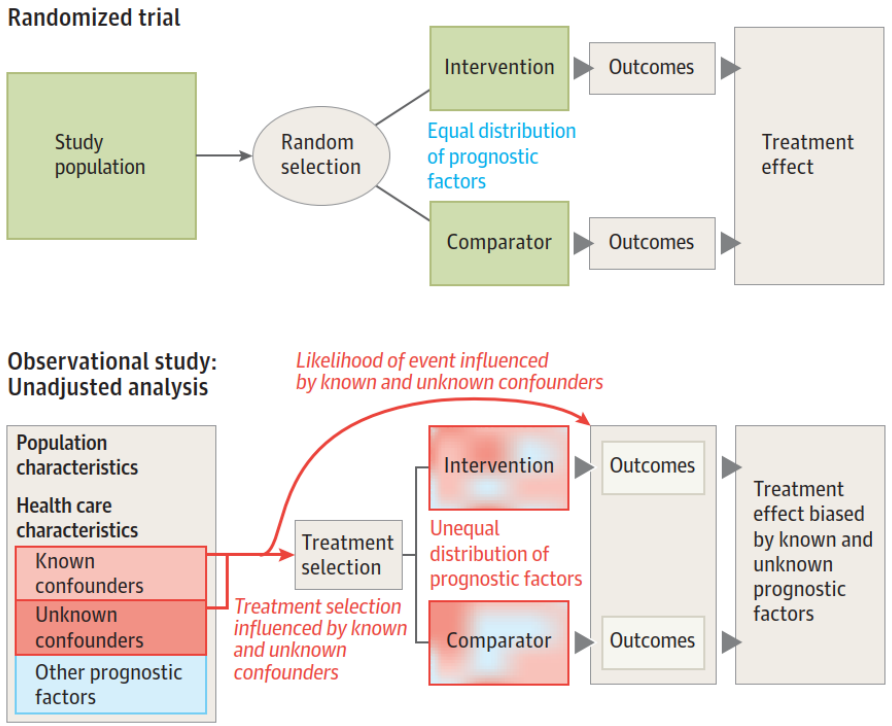
- Not all observational studies are equal.
- However, no statistical approach can account for unmeasured or unknown prognostic factors between groups (residual confounding) and this leaves results susceptible to bias.
- If RCT evidence is not available, it is impossible to determine whether adjusted estimates are accurate or misleading.

Clinical Review & Education

JAMA | Users' Guides to the Medical Literature

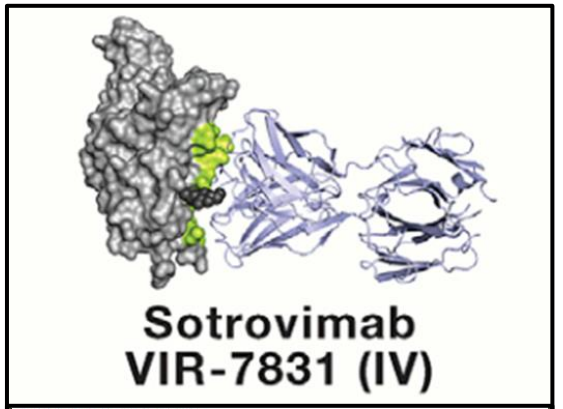
Adjusted Analyses in Studies Addressing Therapy and Harm
Users' Guides to the Medical Literature

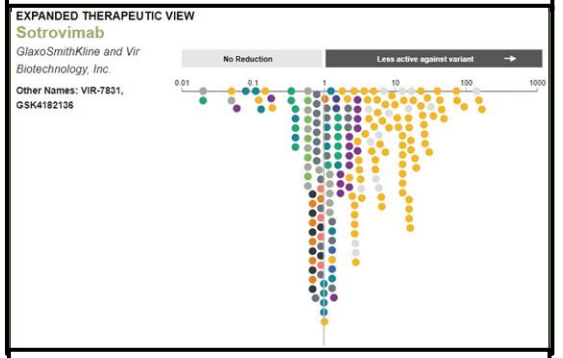
Thomas Agoritsas, MD, PhD; Arnaud Merglen, MD, MSc; Nilay D. Shah, PhD; Martin O'Donnell, MB, PhD; Gordon H. Guyatt, MD, MSc

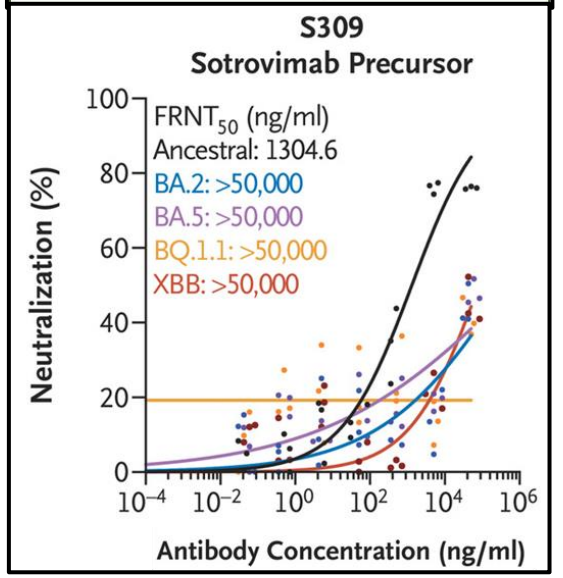


Sotrovimab: preclinical evidence

- Sotrovimab (VIR-7831; GSK4182136) is a is an Fc-engineered IgG neutralizing human monoclonal antibody that binds to an epitope of the SARS-CoV-2 spike protein.
- Antiviral activity in a Syrian Golden hamster model of SARS-CoV-2 infection (Wuhan variant) was demonstrated at 5mg/kg IP but with a version of the antibody that was not Fc-engineered.
- Neutralisation of SARS-CoV-2 (USA WA1/2020) was achieved in Vero E6 cells with an EC_{90} value of 0.19 µg/mL. However, considerable (≥ 20-fold) reduction in neutralisation has been widely documented for all variants since BA.2 Omicron.
- Sotrovimab serum concentrations in COMET-ICE (single 500mg IV infusion) provided geometric mean Cmax (at the end of a 1 hr IV infusion) of 117.6 µg/mL (N=129, CV% 40) and a geometric mean Day 29 serum concentration of 24.5 µg/mL.
- Unlike small molecule drugs monoclonal antibodies have extremely poor penetration into tissue compartments.





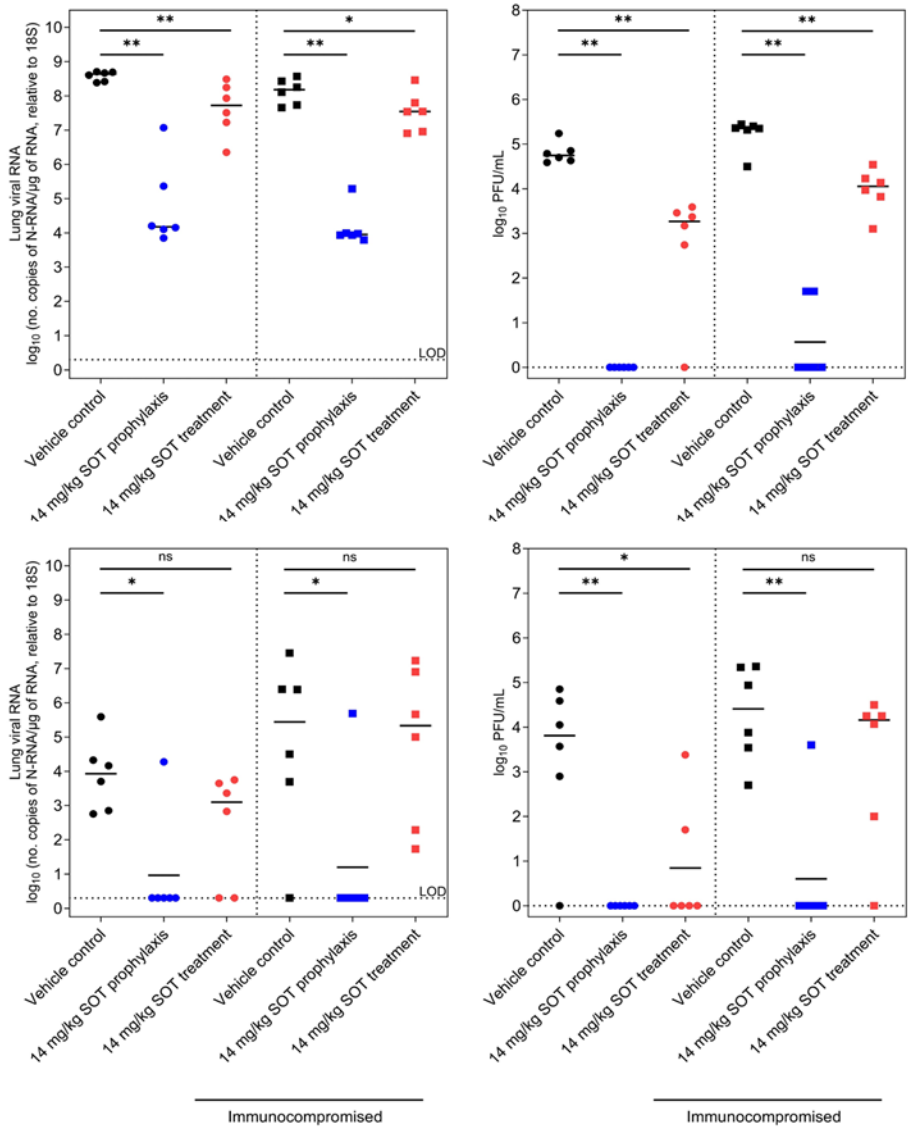


PMC8152891 (VIR authors), https://ca.gsk.com/media/1741008/sotrovimab_pm_en.pdf; https://www.fda.gov/media/149534/download

UNIVERSITY OF LIVERPOOL | CELT

Sotrovimab: preclinical evidence

- Recent preclinical studies showed virological efficacy of sotrovimab against BQ.1.1 in experimental designs reflective of prophylaxis for hamster and non-human primate.
- The bar for efficacy in prophylaxis is lower than the bar for efficacy in treatment.
    - Viral inoculation at maximum antibody concentrations in prophylaxis.
    - Efficacy only needed to suppress replication of very few virion in prophylaxis.
    - Prevention of the upward slope of replication (prophylaxis) versus reduction of high levels of replication (treatment).
- Comparative assessment conducted in Liverpool between:
    - Treatment and prevention
    - Delta and BQ.1.1
    - Immunocompromised versus health hamsters
- No virological efficacy against BQ.1.1 in treatment of immunocompromised hamsters.



Tatham et al. CROI 2024

Sotrovimab: Preclinical PK-PD evidence

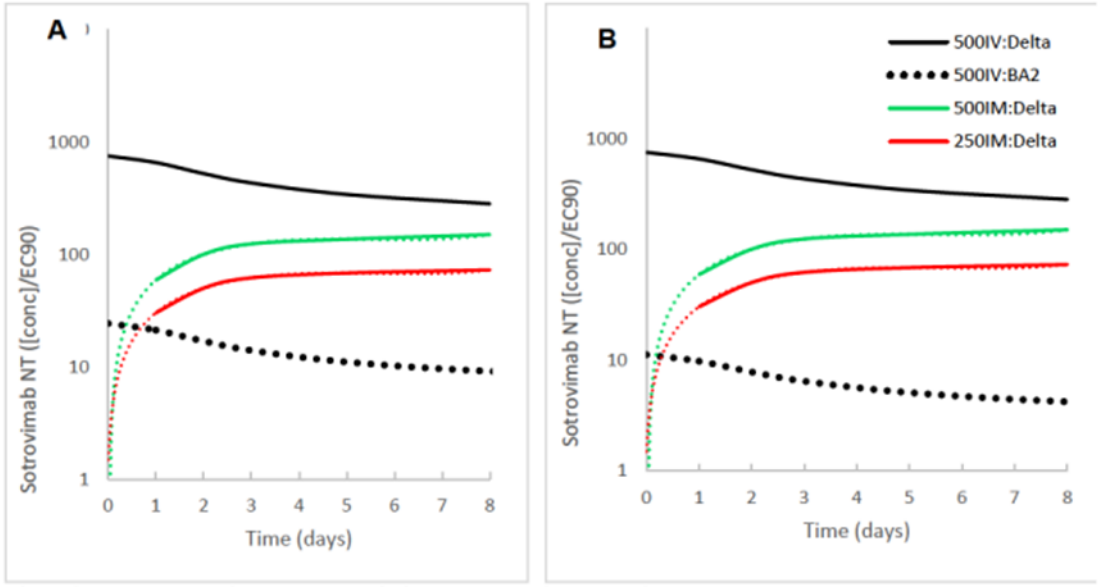
- Direct neutralization of the virus is the primary mechanism of action for monoclonal antibodies. Monoclonal antibodies are selected only on the basis of potency as measured by in vitro neutralization.
- In vitro neutralization measurements are used to define target exposures for clinical development.
- Publicly available information from EMA highlights that 500mg IV provided serum concentrations 15-fold higher than the lung tissue-adjusted EC_{90} (calculated from in vitro neutralization of pre-omicron variants).
- The calculation for target serum exposure included three factors:
    - The in vitro neutralization activity (EC_{90}).
    - An arbitrary tissue penetration for lung.
    - A margin to account for variability in measurements and uncertainty regarding tissue penetration.
- If the same calculation is employed using in vitro neutralization for BA.2 or subsequent Omicron variants, then sotrovimab would be deemed to not reach the serum target.
- Intravenous sotrovimab is dose-linear and dose-proportional.
    - A recommendation in favour of continued efficacy is quantitatively the same as a recommendation in favour of a reduction in dose from 500mg to 25mg for delta.
- Proponents for continued use have argued for a secondary mechanism of action (effector functions), which is plausible but unproven in RCTs.

https://www.ema.europa.eu/en/documents/referral/sotrovimab-also-known-vir-7831-gsk4182136-covid19-article-53-procedure-assessment-report_en.pdf;

Sotrovimab: Clinical PK-PD evidence (RCT derived)

- COMET-TAIL studied 250mg IM, 500mg IM and 500mg IV doses. The independent safety monitoring committee recommended early termination of the 250mg IM arm due to a higher rate of hospitalization than either 500mg IM or 500mg IV dosing.

Figure 3. Sotrovimab Neutralization Titers (NT) Based on Various Sotrovimab IV and IM Doses Normalized to EC_{90} Values for Delta Variant and BA.2 Subvariant

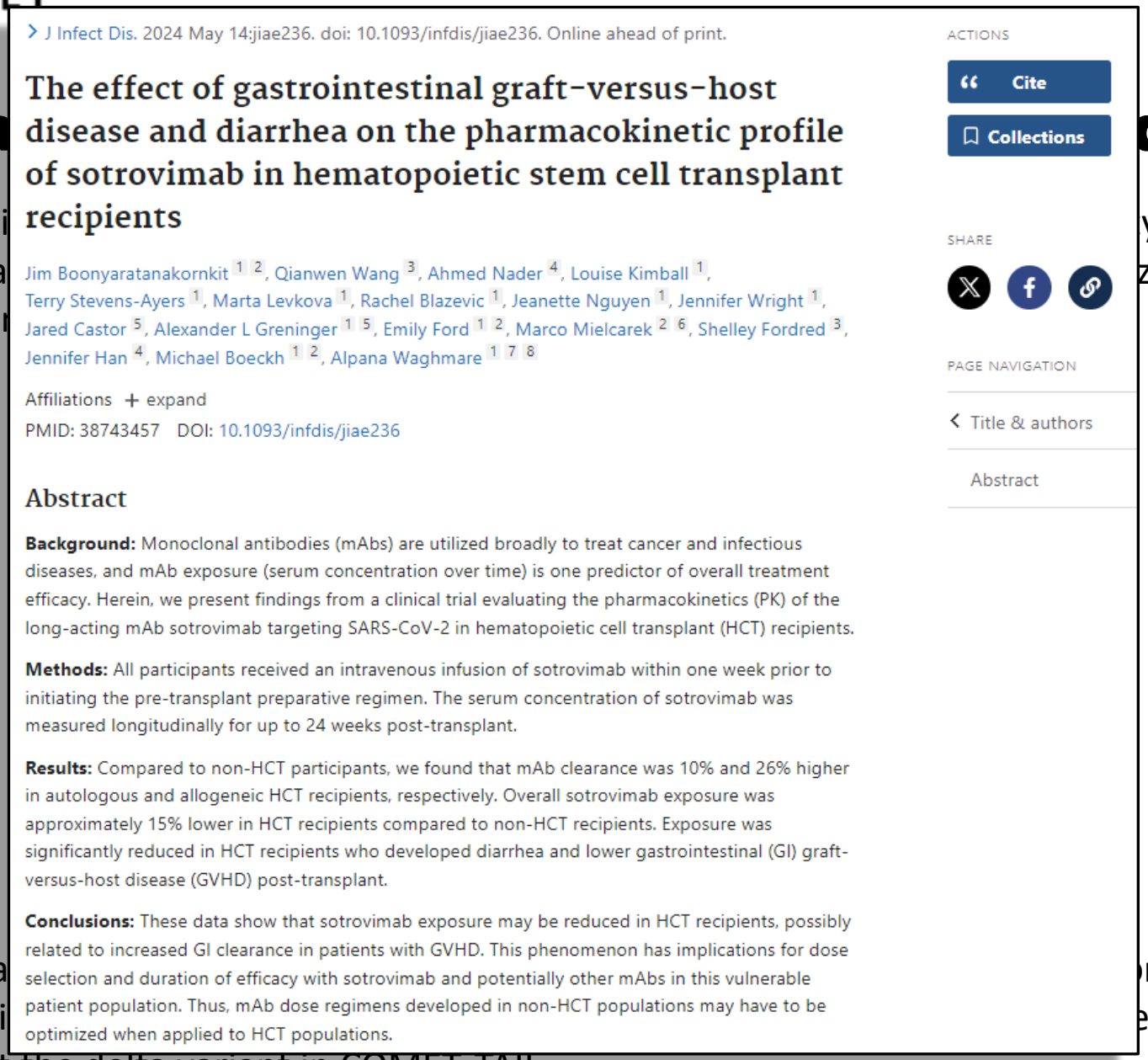


- Based upon this analysis, policymakers with PK-PD expertise (FDA, WHO and others) concluded that a 20-fold or greater reduction in neutralisation would result in titres lower than the suboptimal efficacy observed with 250mg IM against the delta variant in COMET-TAIL.

UNIVERSITY OF LIVERPOOL | CELT

Sotrovima derived)

- COMET-TAIL studi y monitoring committee recommended ea zation than either 500mg IM or 500



J Infect Dis. 2024 May 14:jiae236. doi: 10.1093/infdis/jiae236. Online ahead of print.

The effect of gastrointestinal graft-versus-host disease and diarrhea on the pharmacokinetic profile of sotrovimab in hematopoietic stem cell transplant recipients

Jim Boonyaratanakornkit [1 2], Qianwen Wang [3], Ahmed Nader [4], Louise Kimball [1], Terry Stevens-Ayers [1], Marta Levkova [1], Rachel Blazevic [1], Jeanette Nguyen [1], Jennifer Wright [1], Jared Castor [5], Alexander L Greninger [1 5], Emily Ford [1 2], Marco Mielcarek [2 6], Shelley Fordred [3], Jennifer Han [4], Michael Boeckh [1 2], Alpana Waghmare [1 7 8]

Affiliations + expand

PMID: 38743457 DOI: 10.1093/infdis/jiae236

Abstract

Background: Monoclonal antibodies (mAbs) are utilized broadly to treat cancer and infectious diseases, and mAb exposure (serum concentration over time) is one predictor of overall treatment efficacy. Herein, we present findings from a clinical trial evaluating the pharmacokinetics (PK) of the long-acting mAb sotrovimab targeting SARS-CoV-2 in hematopoietic cell transplant (HCT) recipients.

Methods: All participants received an intravenous infusion of sotrovimab within one week prior to initiating the pre-transplant preparative regimen. The serum concentration of sotrovimab was measured longitudinally for up to 24 weeks post-transplant.

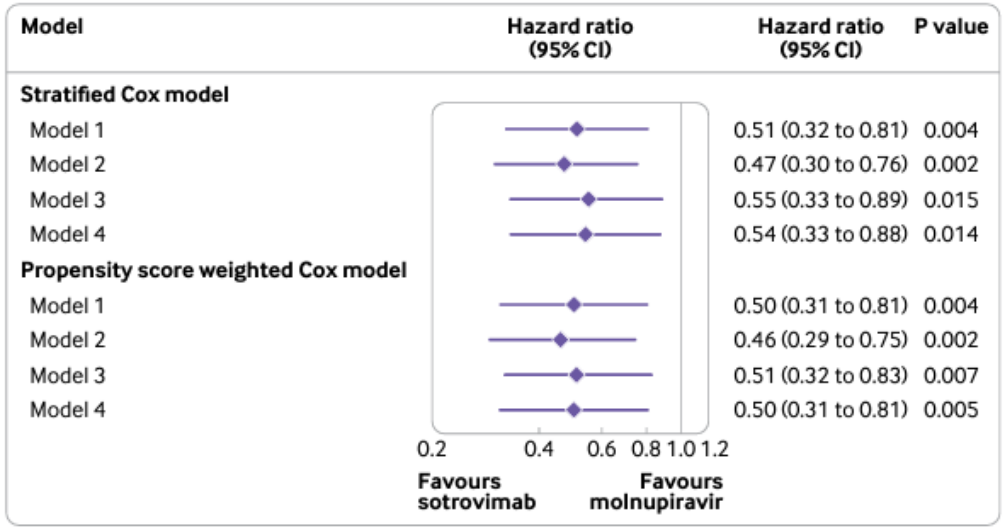
Results: Compared to non-HCT participants, we found that mAb clearance was 10% and 26% higher in autologous and allogeneic HCT recipients, respectively. Overall sotrovimab exposure was approximately 15% lower in HCT recipients compared to non-HCT recipients. Exposure was significantly reduced in HCT recipients who developed diarrhea and lower gastrointestinal (GI) graft-versus-host disease (GVHD) post-transplant.

Conclusions: These data show that sotrovimab exposure may be reduced in HCT recipients, possibly related to increased GI clearance in patients with GVHD. This phenomenon has implications for dose selection and duration of efficacy with sotrovimab and potentially other mAbs in this vulnerable patient population. Thus, mAb dose regimens developed in non-HCT populations may have to be optimized when applied to HCT populations.

- Based upon this a ncluded that a 20-fold or greater reducti fficacy observed with 250mg IM against the delta variant in COMET-TAIL.

Sotrovimab: non-randomized clinical evidence

Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform



- Main analysis conducted during BA.1 predominance (BA.1 neutralisation not anticipated to compromise PK-PD).
- Based upon 87 events (combined endpoint) in 6020 treated patients.
- Did include “exploratory analysis” during BA.2 dominance.

Other observational studies are of variable power and quality but provide conflicting conclusions.

Effectiveness of Sotrovimab and Molnupiravir in community settings in England across the Omicron BA.1 and BA.2 sublineages: emulated target trials using the OpenSAFELY platform

The OpenSAFELY collaborative: John Tazare[1*], Linda Nab[2*], Bang Zheng[1], William J Hulme[2], Amelia C A Green[2], Helen J Curtis[2], Viyaasan Mahalingasivam[1], Rose Higgins[2], Anna Schultze[1], Krishnan Bhaskaran[1], Amir Mehrkar[2], Andrea Schaffer[2], Rebecca M Smith[2], Christopher Bates[3], Jonathan Cockburn[3], John Parry[3], Frank Hester[3], Sam Harper[3], Rosalind M Eggo[1], Alex J Walker[2], Michael Marks[1,4,5], Mike Brown[1,4], Camille Maringe[1], Clémence Leyrat[1], Stephen J W Evans[1], Ben Goldacre[2], Brian MacKenna[2], Jonathan A C Sterne[6,7,*], Laurie A Tomlinson[1,*], Ian J Douglas[1,*]

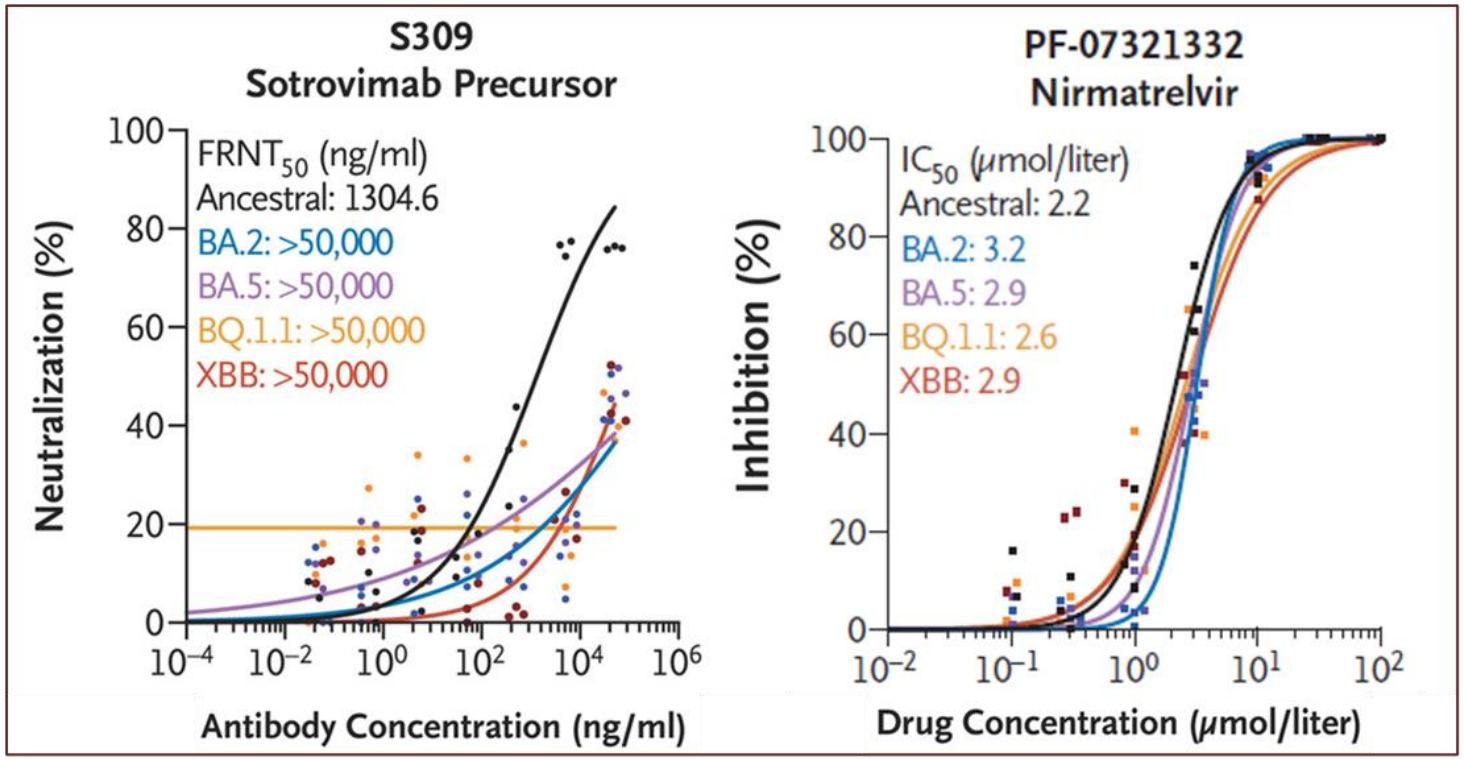
Results

Of the 35,856 [BA.1 period] and 39,192 [BA.2 period] patients, 1,830 [BA.1] and 1,242 [BA.2] were treated with molnupiravir and 2,244 [BA.1] and 4,164 [BA.2] with sotrovimab. The estimated HRs for molnupiravir versus untreated were 1.00 (95%CI: 0.81;1.22) [BA.1] and 1.22 (0.96;1.56) [BA.2]; corresponding HRs for sotrovimab versus untreated were 0.76 (0.66;0.89) [BA.1] and 0.92 (0.79;1.06) [BA.2].

Interpretation

Compared with no treatment, sotrovimab was associated with reduced risk of adverse outcomes after COVID-19 in the BA.1 period, but there was weaker evidence of benefit in the BA2 period. Molnupiravir was not associated with reduced risk in either period.

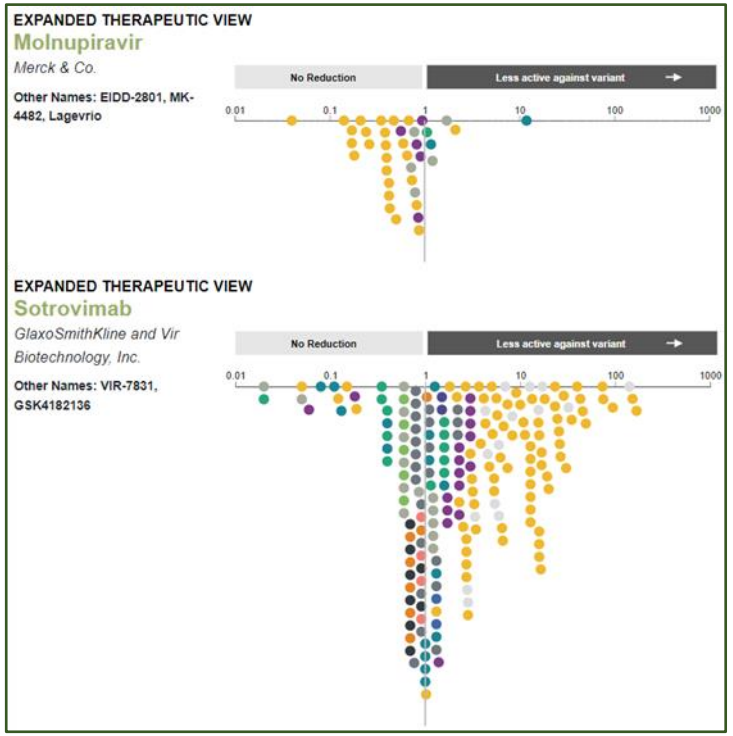
Nirmatrelvir / ritonavir: activity across variants

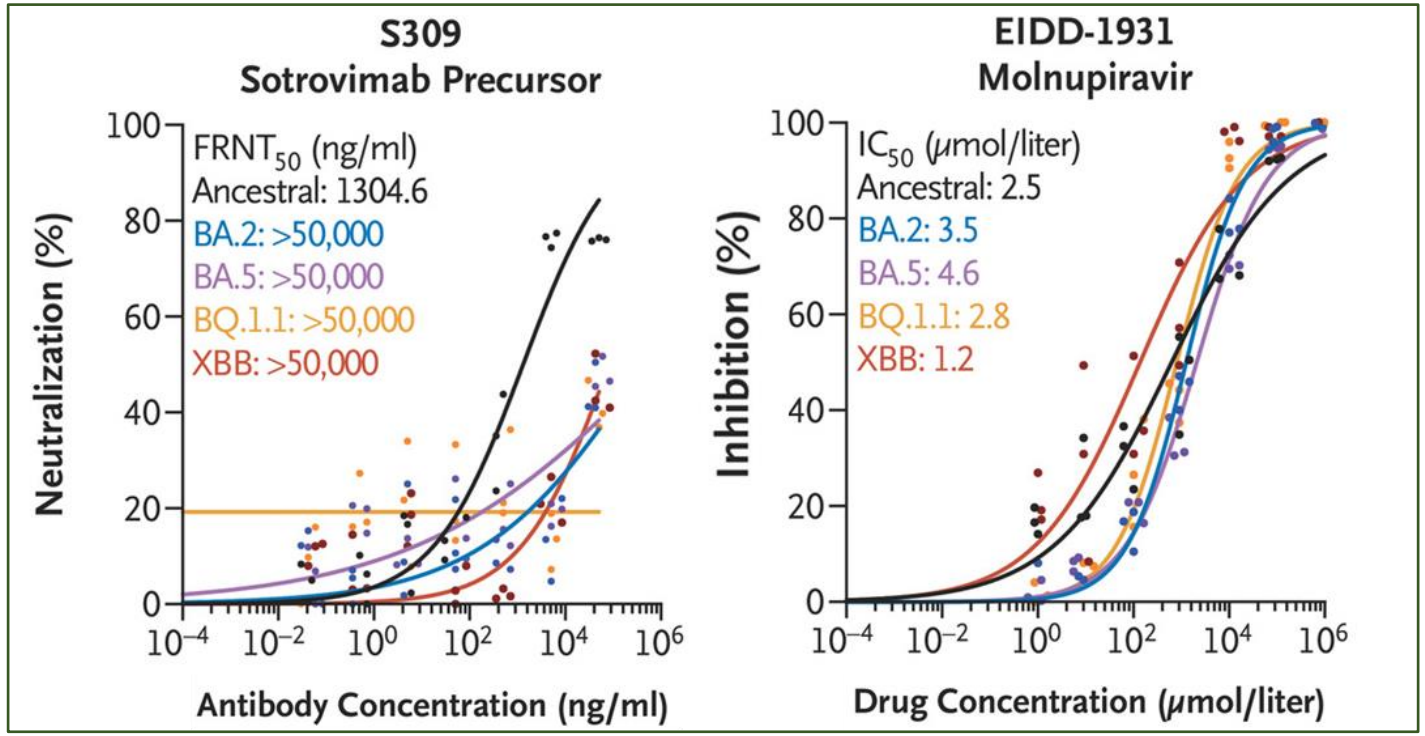


- Major differences across variants have occurred in the viral spike protein and not the protease that is targeted by nirmatrelvir.
- Accordingly, nirmatrelvir activity across variants has been stable in comparison to monoclonal antibodies that target the spike protein.
- Therefore, there is no known molecular of pharmacokinetic-pharmacodynamic basis for a change in activity of nirmatrelvir since pivotal RCTs were conducted.

https://opendata.ncats.nih.gov/variant/activity; https://www.nejm.org/doi/full/10.1056/NEJMc2214302

Molnupiravir: activity across variants





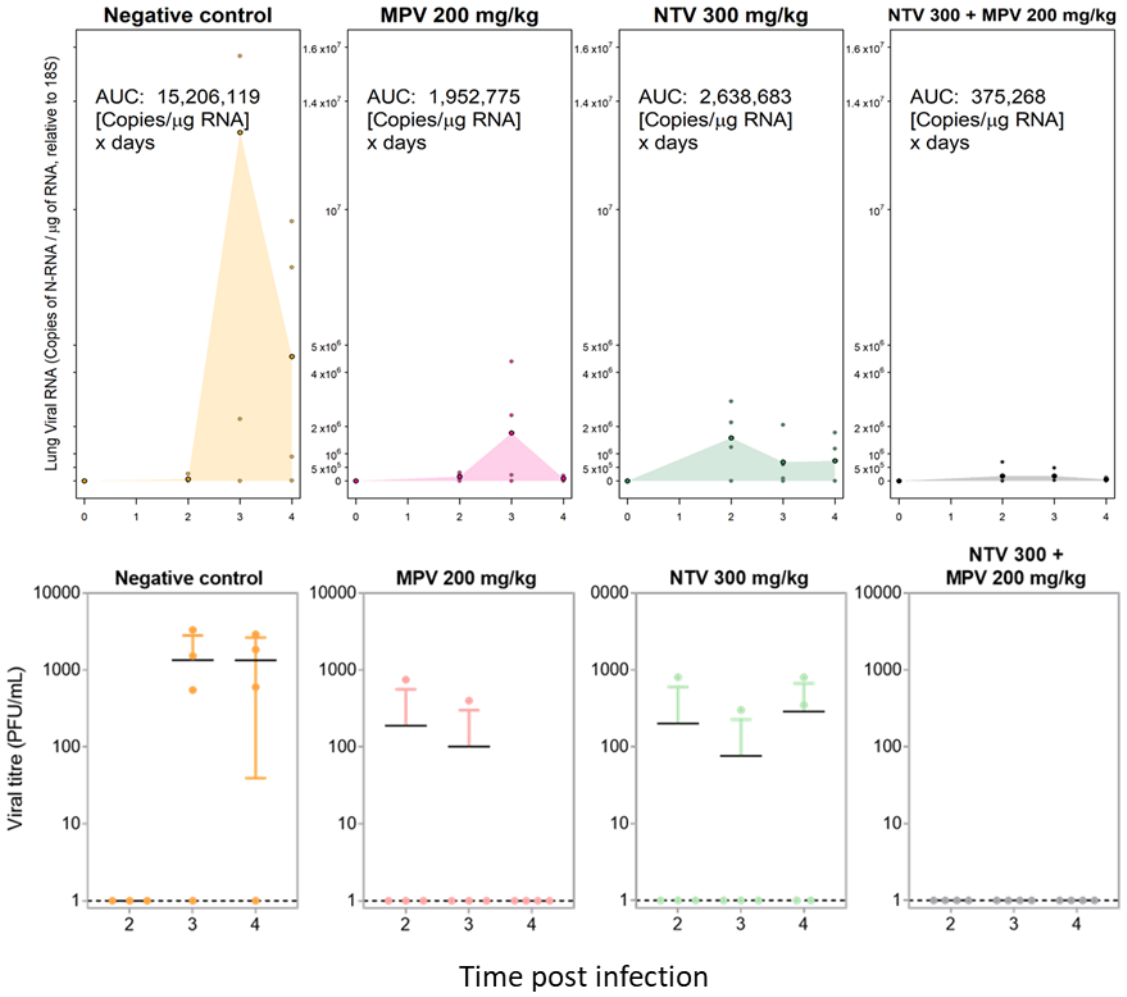
- Major differences across variants have occurred in the viral spike protein and not the RNA polymerase that is targeted by molnupiravir.
- Accordingly, molnupiravir activity across variants has been stable in comparison to monoclonal antibodies that target the spike protein.
- Therefore, there is no known molecular of pharmacokinetic-pharmacodynamic basis for a change in activity of molnupiravir since pivotal RCTs were conducted.

https://opendata.ncats.nih.gov/variant/activity; https://www.nejm.org/doi/full/10.1056/NEJMc2214302

UNIVERSITY OF LIVERPOOL | CELT

What is the evidence for antiviral combinations?

- Successful treatments for other viruses (HIV and HCV) involve use of potent drug combinations.
- Virological efficacy of nirmatrelvir (NTV) and molnupiravir (MPV) individually or in combination against BA.1 Omicron in K18-hACE2 mice.
- Lung viral RNA was lower in the combination group, than when either drug was dosed alone (statistical significance was not reached).
- The combination group was the only group in replicative virus (plaque assay) could not be detected in any animal.
- Combinations offer potential for higher efficacy, higher resilience against emergent variants and mitigation of the resistance risk.



Tatham et al. CROI 2023

Summary and conclusions

- Principles of antiviral pharmacology were borne out in the accelerated development of antivirals for SARS-CoV-2.
- It should not be contentious that an antiviral intervention needs to reach antiviral concentrations at its target site in order to exert antiviral efficacy (but it is in some cases).
- Small molecule drugs have proven resilient to changes in the virus over time. All monoclonal antibodies have been compromised to some degree.

	PK-PD assessment	Preclinical efficacy	RCT data	Observational data
Molnupiravir	Supports continued efficacy	Supports continued efficacy	Supports efficacy (no change since pivotal)	Predominantly supports efficacy
Nirmatrelvir	Supports continued efficacy	Supports continued efficacy	Supports efficacy (no change since pivotal)	Predominantly supports efficacy
Sotrovimab	Does not support efficacy	Does not support efficacy (in treatment)	None (pivotal data are indirect)	Mixed and variable outcomes (and low numbers)

- Continued efficacy of sotrovimab remains highly uncertain but a definitive outcome is critically needed:
    - Should we be using medicines with unknown efficacy?
    - Was the dose really ≥ 20-fold higher than it needed to be for pre-Omicron variants? If so, we really need to understand the PK-PD to improve equity and accessibility of other MAbs in LMIC.