Science Advances
AAAS

advances.sciencemag.org/cgi/content/full/sciadv.abc7112/DC1

Supplementary Materials for

Potency and timing of antiviral therapy as determinants of duration of SARS-CoV-2 shedding and intensity of inflammatory response

Ashish Goyal, E. Fabian Cardozo-Ojeda, Joshua T. Schiffer*

*Corresponding author. Email: jschiffe@fredhutch.org

Published 23 October 2020, *Sci. Adv.* **6**, eabc7112 (2020)
DOI: 10.1126/sciadv.abc7112

This PDF file includes:

Supplement

Fig S1. Mathematical model recapitulation of untreated SARS-CoV-2 kinetics with assumed neutralizing antibody effect. Model fit to individual data. Shapes are individual viral loads and lines are model load projections. S = Singapore; G = Germany; K = South Korea; F = France. Projections are nearly equivalent to those with acquired cytolytic immunity **(Fig 1)**.

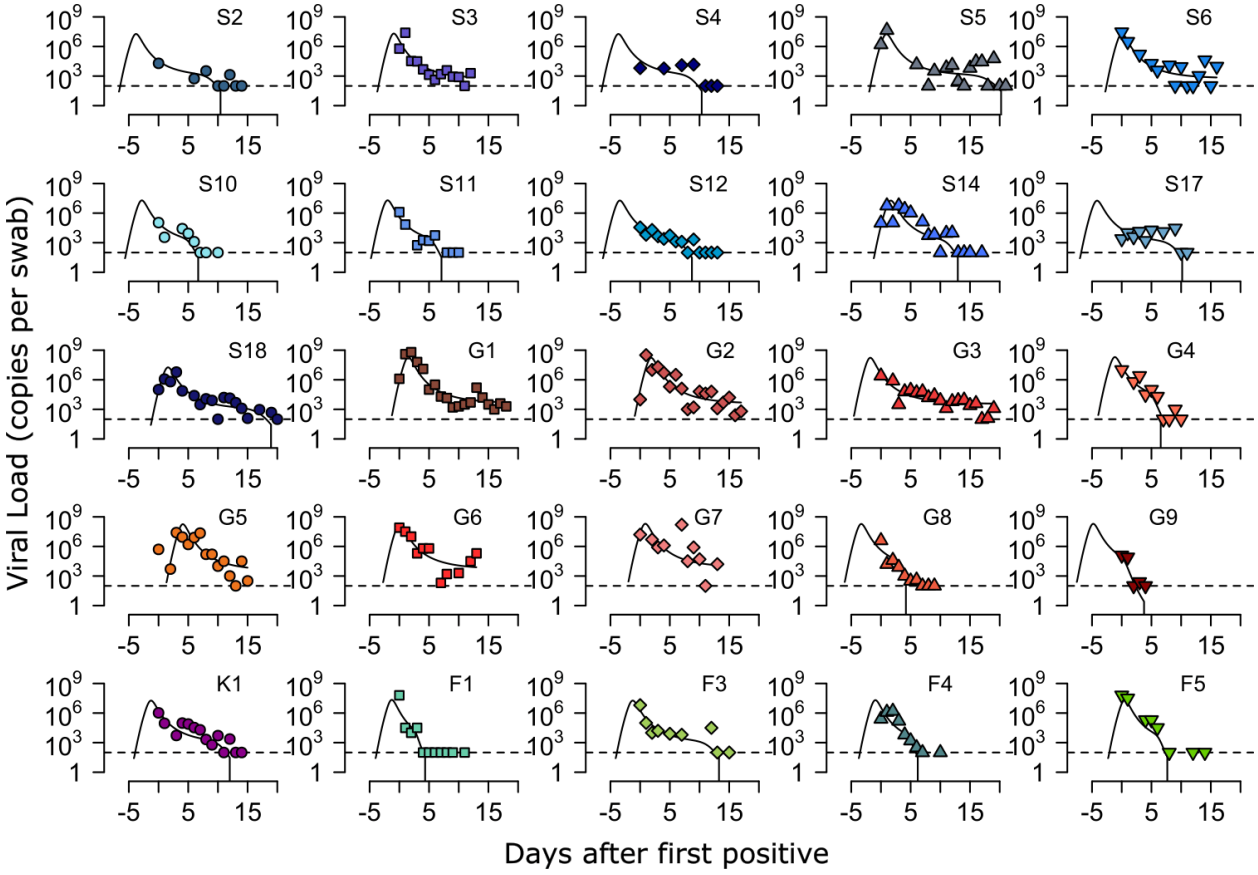

Fig S2. Treatment projections of a 5-day remdesivir course assuming different potency and timing of treatment. Each set of simulations is performed under assumptions of high, medium and low potency (EC50=0.8, 8 and 80 uM respectively). Treatment initiation is at timepoints generally consistent with **A.** hospitalization (day 10 after first positive sample), **B.** first symptoms (day 5 after first positive sample), **C.** pre-symptomatic post-peak phase (day 2 after first positive sample) and **D.** pre-symptomatic pre-peak phase (day 0). Overall, early potent treatment limits duration of infection. Prolonged shedding is predicted as a possibility with sub-potent, early initiation of therapy due to inadequate activation of immunity.

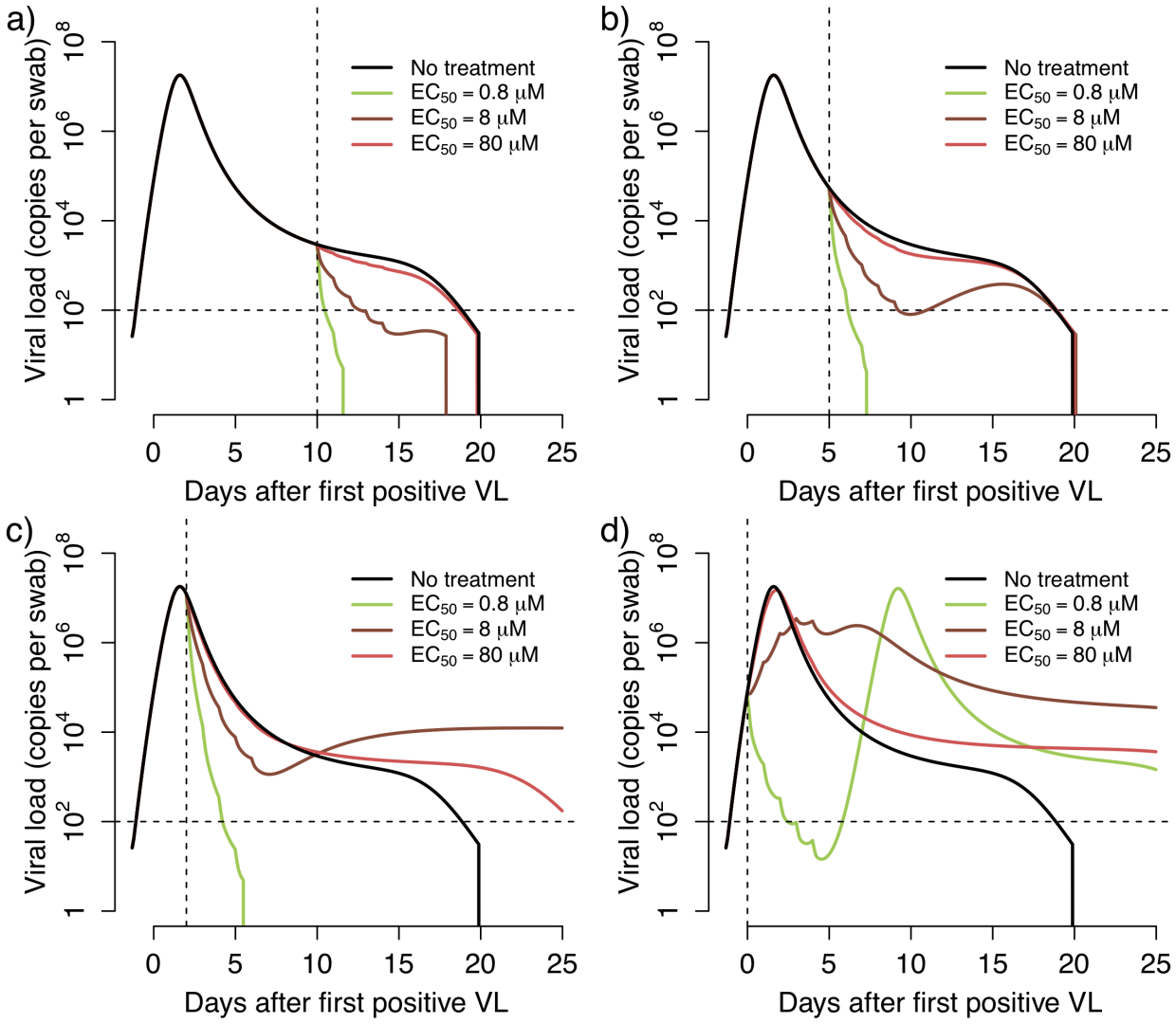

Fig S3. Projections of remdesivir drug resistance during therapy. Simulations are with high potency (EC50=0.8 uM) and the assumption that mutants confer complete drug resistance. Treatment initiation is at timepoints generally consistent with hospitalization (day 10 after first positive sample), first symptoms (day 5 after first positive sample), pre-symptomatic post-peak phase (day 2 after first positive sample) or pre-symptomatic pre-peak phase (day 0). **A.** Projections of no treatment, treatment with no assumed drug resistance, and treatment with assumed drug resistance. **B.** Projections of assumed drug resistance with trajectories of sensitive strains and single mutants displayed. Prolonged shedding is predicted as a possibility with sub-potent, early initiation of therapy due to inadequate activation of immunity.

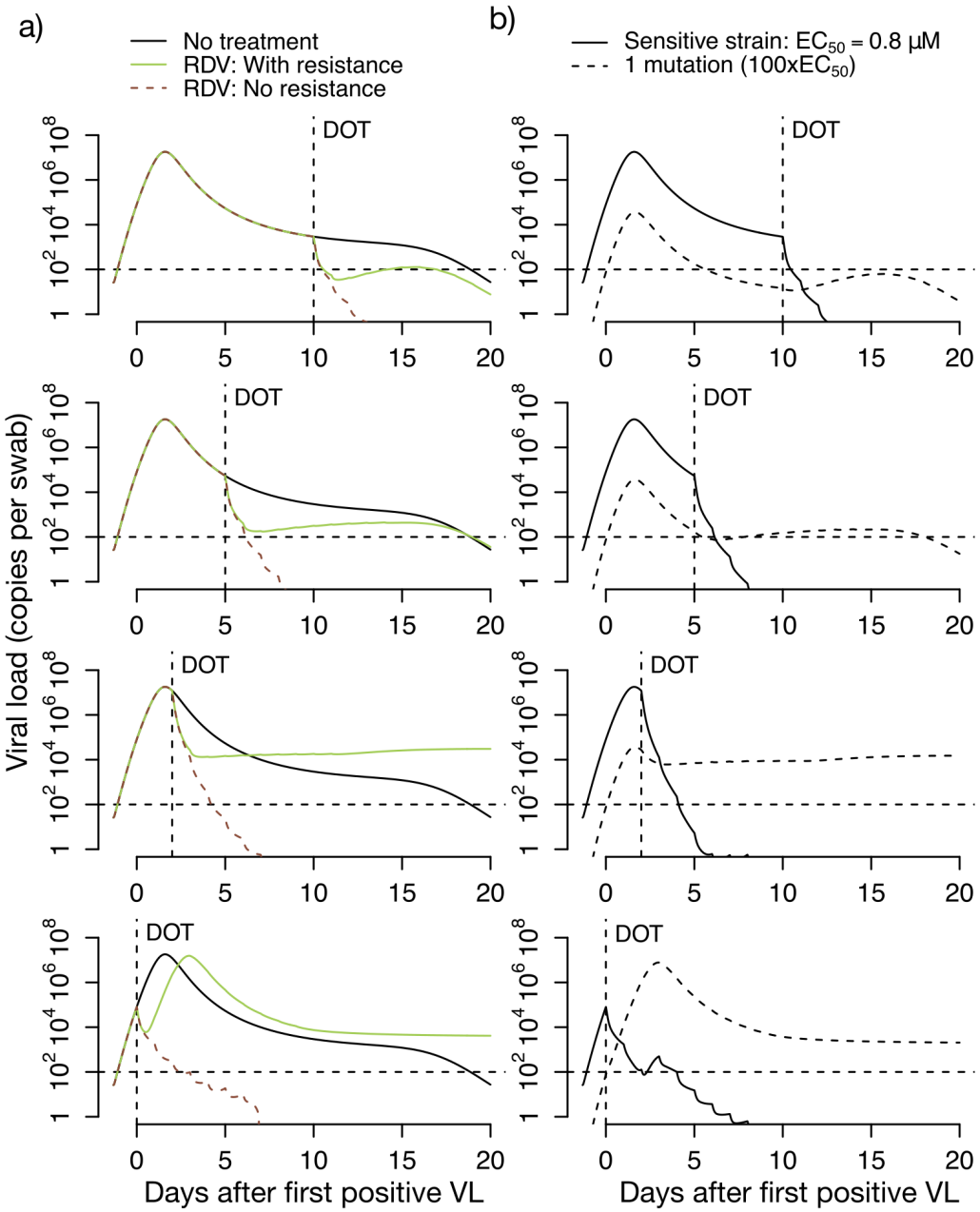

Fig S4. Treatment projections of selinexor assuming different potency and timing of treatment. Each set of simulations is performed under assumptions of high, medium and low potency. Treatment initiation is at timepoints generally consistent with **A.** hospitalization (day 10 after first positive sample), **B.** first symptoms (day 5 after first positive sample), **C.** pre-symptomatic post-peak phase (day 2 after first positive sample) and **D.** pre-symptomatic pre-peak phase (day 0). Overall, early potent treatment limits duration of infection. Prolonged shedding is predicted as a possibility with sub-potent, early initiation of therapy due to inadequate activation of immunity.

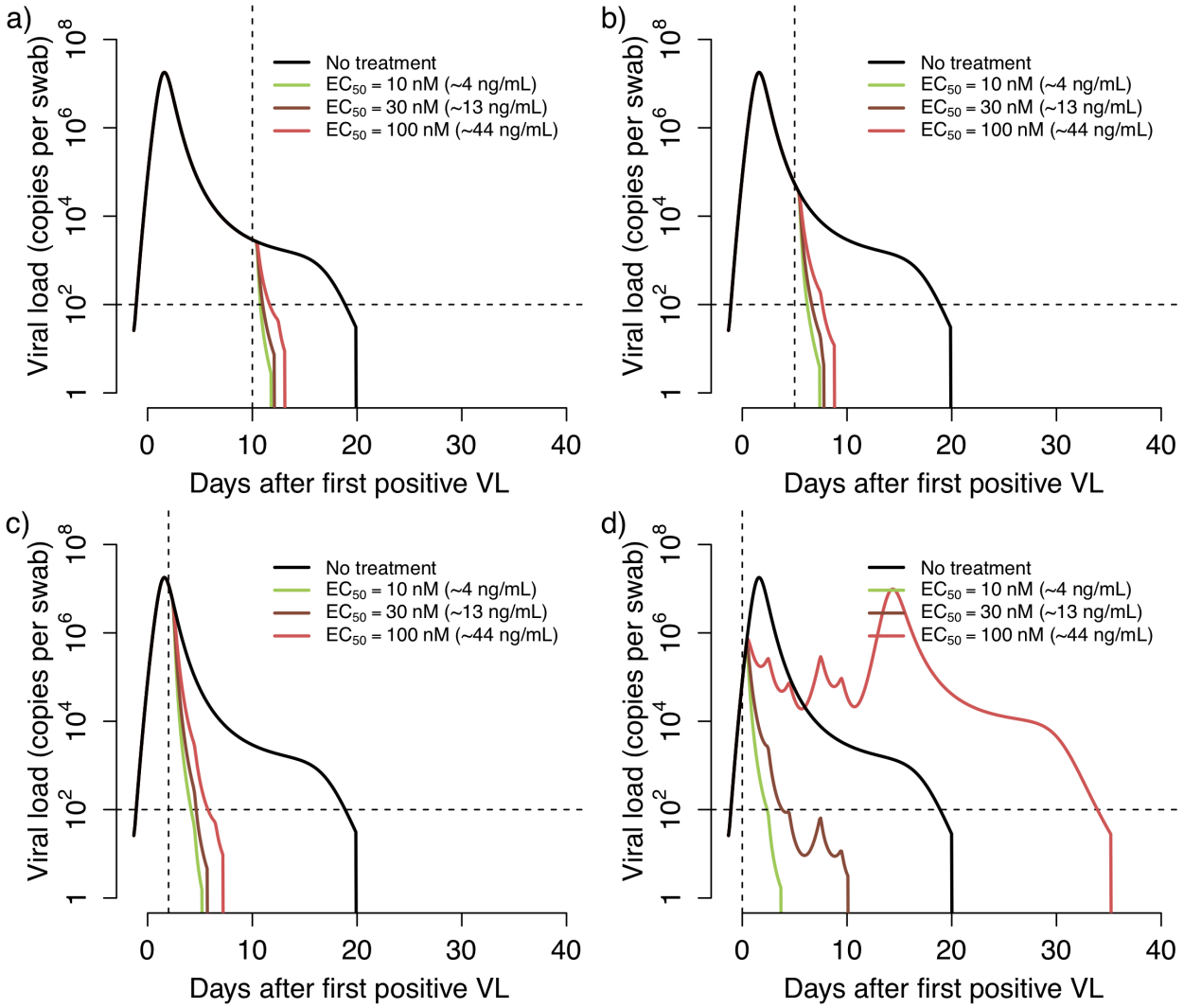

Fig S5. Treatment projections of broadly neutralizing antibody (bNab) assuming different potency and timing of treatment. Each set of simulations is performed under assumptions of high, medium and low potency. Treatment initiation is at timepoints generally consistent with **A.** hospitalization (day 10 after first positive sample), **B.** first symptoms (day 5 after first positive sample), **C.** pre-symptomatic post-peak phase (day 2 after first positive sample) and **D.** pre-symptomatic pre-peak phase (day 0). Overall, early potent treatment limits duration of infection. Prolonged shedding is predicted as a possibility with sub-potent, early initiation of therapy due to inadequate activation of immunity. Heatmaps comparing variability in bNAb potency measured by *in vivo* EC50 (x-axis) and timing of treatment initiation (y-axis) for **E.** shedding duration, **F.** viral load area under the curve (AUC) and **G.** extent of T cell response required for viral elimination.

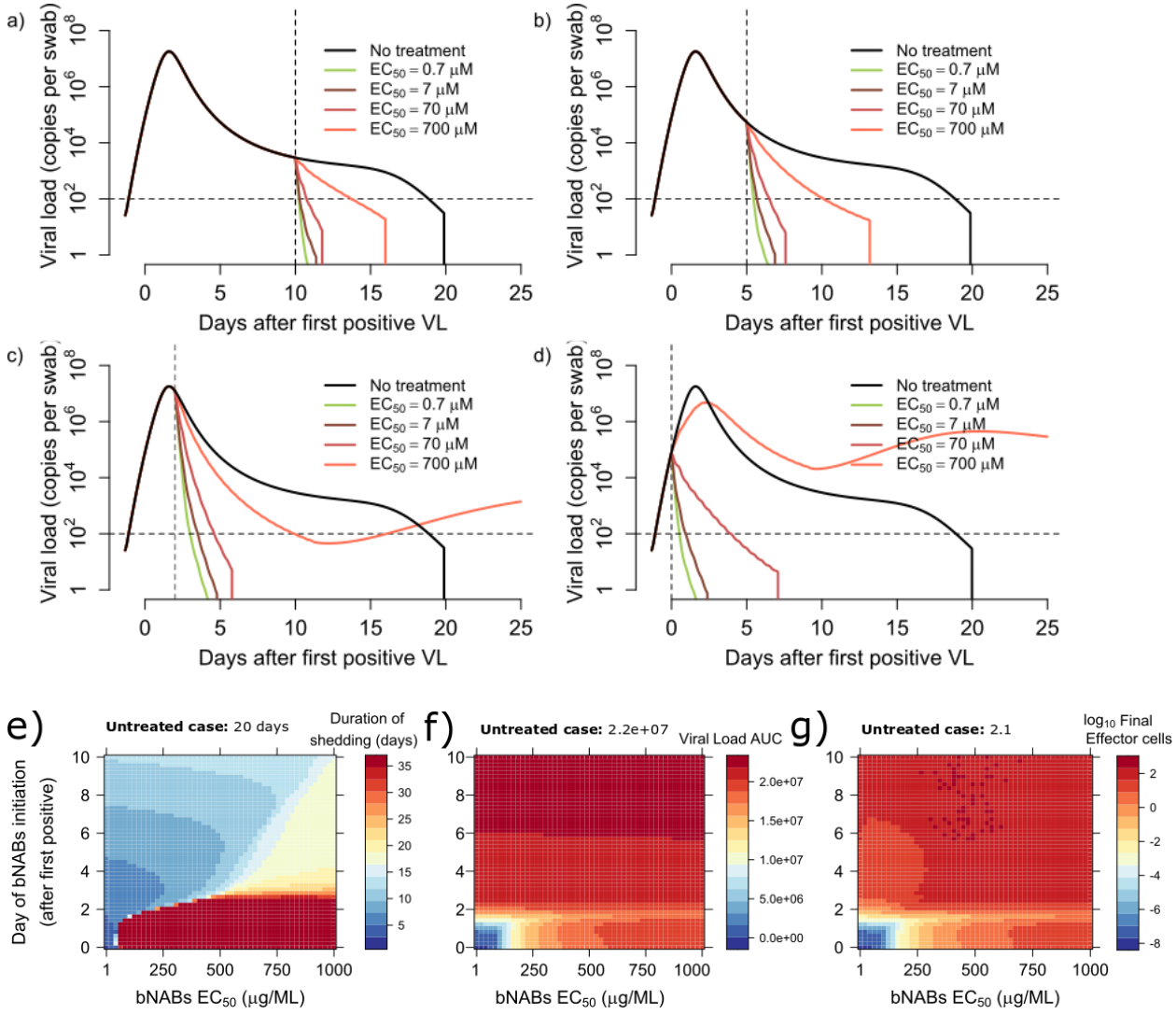

Table S1: Akaike information criterion (AIC) for multiple instances of our model with different number of the compartments of M (n) and the hill-coefficient associated the effector cell response (r). A lower AIC better supports the combination of parameters for our model. We found that $n = 2$ and $r = 10$ is best supported by the data (bold red). We also tried a model with $n = 0$ (i.e., no effector cell response), and a model with $n = 0$ and $k = 0$. In both cases, we found AIC~945, supporting the choice of our model.

	$r = 0.1$	$r = 1$	$r = 5$	$r = 10$	$r = 15$
$n = 1$	922.8	935.4	929.7	926.5	932.2
$n = 2$	929.2	924.0	941.6	**919.9**	925.9
$n = 3$	922.8	935.4	929.7	926.5	932.2
$n = 4$	951.5	928.6	925.8	925.5	924.3
$n = 5$	950.4	930.8	929.1	923.3	922.5
$n = 6$	NA	928.6	926.0	924.9	923.2
$n = 7$	NA	928.3	926.4	927.8	924.8

Table S2. Individual parameter estimates for the best model fits to the viral load data (lowest AIC in Table S1). * represent parameter value that was not estimated and fixed as a prior during parameter estimation.

ID	t_{init} (days before 1st +)	$\log_{10}\beta$ (virions^{-1} day^{-1})	δ (day^{-1} cells^{-k})	k (-)	$\log_{10}\pi$ ($\log_{10}$ day^{-1})	m (day^{-1} cells^{-1})	$\log_{10}\omega$ (day^{-1} cells^{-1})	q (day^{-1})
S2	-6.68	-7.23	3.14	0.08	2.59	2.91	-4.56	2.4E-05
S3	-3.73	-7.22	3.12	0.08	2.60	0*	-4.55	2.4E-05
S4	-6.56	-7.23	3.14	0.08	2.59	3.51	-4.56	2.4E-05
S5	-2.00	-7.23	3.15	0.08	2.59	3.31	-4.56	2.4E-05
S6	-2.79	-7.23	3.12	0.08	2.60	0*	-4.55	2.4E-05
S10	-5.66	-7.23	3.13	0.08	2.59	3.54	-4.55	2.4E-05
S11	-4.80	-7.23	3.13	0.08	2.60	3.51	-4.56	2.4E-05
S12	-6.29	-7.23	3.14	0.08	2.59	3.26	-4.56	2.4E-05
S14	-1.23	-7.23	3.13	0.08	2.59	3.57	-4.55	2.4E-05
S17	-7.06	-7.23	3.14	0.08	2.59	3.39	-4.56	2.4E-05
S18	-1.32	-7.23	3.15	0.08	2.59	3.20	-4.56	2.4E-05
G1	-1.27	-7.22	3.12	0.08	2.60	0*	-4.55	2.4E-05
G2	-0.92	-7.22	3.12	0.08	2.60	0*	-4.55	2.4E-05
G3	-4.57	-7.22	3.12	0.08	2.60	0*	-4.55	2.4E-05
G4	-3.97	-7.23	3.12	0.08	2.60	3.13	-4.55	2.4E-05
G5	1.32	-7.22	3.12	0.08	2.60	0*	-4.55	2.4E-05
G6	-2.76	-7.23	3.13	0.08	2.60	0*	-4.55	2.4E-05
G7	-2.00	-7.23	3.13	0.08	2.59	0*	-4.55	2.4E-05
G8	-6.12	-7.23	3.12	0.08	2.60	3.21	-4.55	2.4E-05
G9	-7.58	-7.22	3.11	0.08	2.60	3.72	-4.55	2.4E-05
K1	-4.17	-7.23	3.14	0.08	2.59	3.30	-4.56	2.4E-05
F1	-4.02	-7.22	3.10	0.08	2.60	4.06	-4.55	2.4E-05
F3	-4.14	-7.23	3.14	0.08	2.59	3.36	-4.56	2.4E-05
F4	-3.74	-7.23	3.11	0.08	2.60	3.45	-4.55	2.4E-05
F5	-2.31	-7.23	3.11	0.08	2.60	3.54	-4.55	2.4E-05

Table S3. Individual parameter estimates for pharmacokinetics model of remdesivir.

Parameter	Value
k_{pa}	21 day^{-1}
k_c	29 day^{-1}
k_a	1.2 day^{-1}
V_1	2.84 L. Molecular mass
V_2	0.12 L. Molecular mass

Table S4. Parameter estimates for pharmacokinetics model of selinexor.

Parameter	Value
k_a	6.1 day^{-1}
k_c	229 day^{-1}
k_{12}	2×10^6 day^{-1}
k_{21}	1.5×10^4 day^{-1}
k_{13}	6.5×10^2 day^{-1}
k_{31}	0.85 day^{-1}
V_1	0.002 mL
V_2	0.5 mL
V_3	1.6 mL