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Viral Dynamic Models Provide an Explanation for SARS-CoV-2 Rebound After Nirmatrelvir

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BACKGROUND

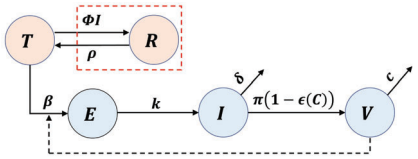
- A 5-day course of nirmatrelvir/ritonavir is recommended for individuals who test positive for SARS-CoV-2
- Treatment is suggested to be initiated as soon as possible
- In some cases, viral rebound and recurring symptoms occur after the 5-day treatment

Question: Why is the viral rebound observed in some patients?

Hypothesis: Paxlovid treatment halts the depletion of target cells without fully eliminating the virus, leading to viral rebound.

METHODS

- Data from 3 people with well-characterized rebound.[1]
- Accurate PK/PD absorption/elimination model.[2]
- Fitted viral dynamic models to study cause of rebound.[3-5]
- Thousands of simulations to characterize rebound sensitivity of model parameters.



Standard viral dynamic model

$$\frac{dT}{dt} = -\beta VT$$
$$\frac{dE}{dt} = \beta VT - kE$$
$$\frac{dI}{dt} = kE - \delta(t)I$$
$$\frac{dV}{dt} = (1-\epsilon(C))\pi I - cV$$

$$\delta(t) = \begin{cases} \delta_0 & \text{for } t < t^* \\ \delta_0 e^{\sigma(t-t^*)} & \text{for } t \geq t^* \end{cases}$$

Viral dynamic model with innate immune response

$$\frac{dT}{dt} = -\beta VT - \phi IT + \rho R$$
$$\frac{dR}{dt} = \phi IT - \rho R$$
$$\frac{dE}{dt} = \beta VT - kE$$
$$\frac{dI}{dt} = kE - \delta(t)I$$
$$\frac{dV}{dt} = (1-\epsilon(C))\pi I - cV$$

RESULTS

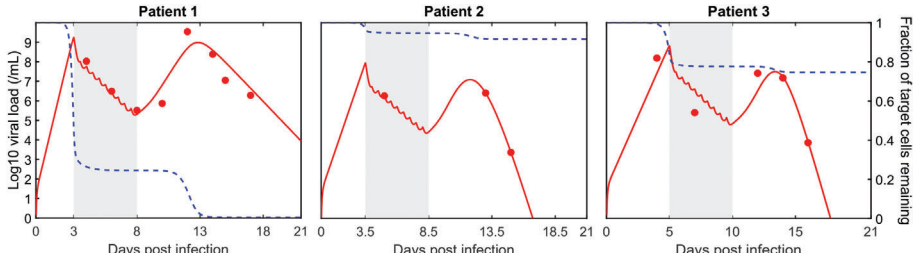


Figure 1. Viral dynamics and rebound can be captured by both viral dynamic models. Target cell depletion (dashed lines) is temporarily halted following treatment initiation. The remaining target cells can support viral replication if there is viable virus remaining after treatment.

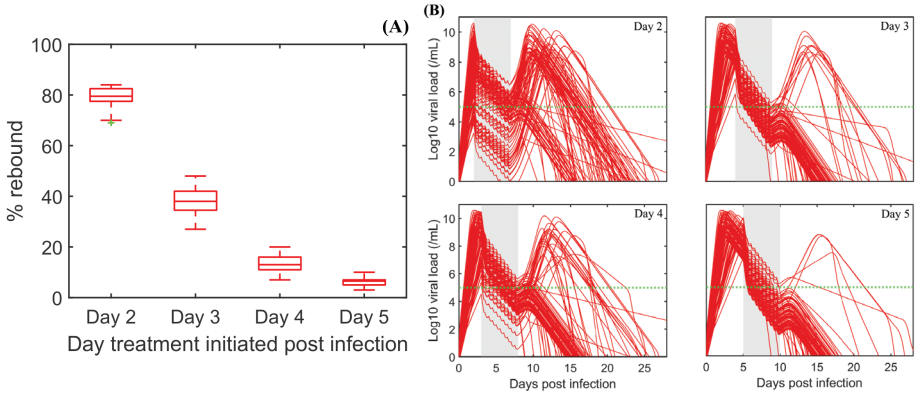


Figure 2. Viral rebound is sensitive to model parameters. However, in general, models predict that earlier treatment corresponds to a higher fraction of rebound cases.

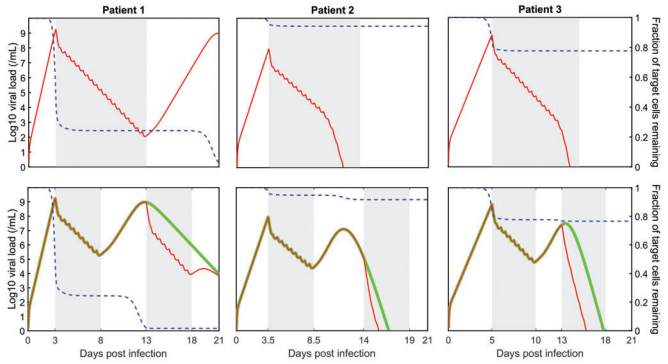


Figure 3. Alternative treatment strategies need to account for the availability of target cells, drug effectiveness, and adaptive immunity to prevent rebound.

CONCLUSIONS

- Nirmatrelvir preserves target cells, but does not eliminate the virus in cases with viral rebound.
- The time therapy is initiated is critical with earlier treatment predicted to lead to higher probability of rebound (this may explain why so many high profile people have experience this rebound)
- The individual's viral dynamic parameters, and the timing of adaptive immunity also play important roles.

- Increasing the length of treatment from 5 to 10 days will continue to preserve target cells and thus may still allow viral rebound.
- However, longer treatment could allow a vigorous adaptive immunity, which is critical to clear the virus.
- An additional course of treatment 1 day after symptom rebound makes little difference in the viral clearance time.

- Delaying treatment may reduce the probability of rebound, but at the cost of possible detrimental effects in disease severity and increased viral transmission.

- Rebound following antiviral treatment is not unique to nirmatrelvir and occurs with molnupiravir presumably for similar reasons[6].

ADDITIONAL KEY INFORMATION

References

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