Detection of significant antiviral drug effects on COVID-19 with reasonable sample sizes in randomized controlled trials: A modeling study

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INTRODUCTION

The development of effective antiviral treatments for COVID-19 is a global health priority. With the urgency of developing new antiviral drugs and repurposing existing approved antivirals, clinical studies, including compassionate use programs, have often yielded inconsistent or nonsignificant results, possibly due to rushed study designs, clinical confounders, and varying patient responses.

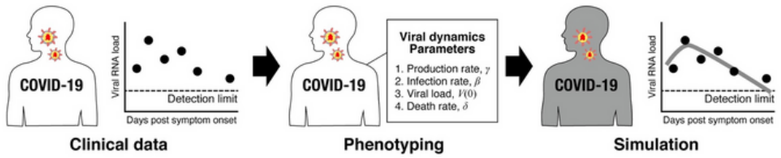
This study aims to investigate the underlying reasons for these inconsistencies by applying a virus dynamics model to clinical data. Our findings suggest that two key factors may obscure the effectiveness of antiviral drugs in clinical settings: 1) Patient-to-patient variability in virus dynamics, and 2) Delayed treatment initiation.

We also propose a novel method to calculate the minimum sample size required for clinical trials, accounting for these factors in virus dynamics, to improve the reliability of trial results

METHODOLOGY

Study data: The longitudinal viral load data measured from upper respiratory specimens were extracted from the published studies of SARS-CoV-2. Patients who received antiviral treatment and for whom data were measured on only 1 or 2 days were excluded. 30 patients' data were used in total.

Methods: The data were analyzed by the mathematical model(Eq1,2), and virus dynamics parameters were estimated for each patient (i.e., phenotyping).



$$\frac{df(t)}{dt} = -\beta f(t)V(t),$$

$$\frac{dV(t)}{dt} = \gamma f(t)V(t) - \delta V(t),$$

Eq 1, 2: SARS-CoV-2 virus dynamics without antiviral treatment, f(t) is the relative fraction of uninfected target cells at time t to those at time 0, and $V(t)$ is the amount of virus at time t

$$\frac{df(t)}{dt} = -\beta f(t)V(t),$$

$$\frac{dV(t)}{dt} = (1 - \varepsilon \times H(t))\gamma f(t)V(t) - \delta V(t),$$

The virus dynamic model under antiviral treatment (which we assume blocks virus replication) initiated at t* days after symptom onset, where H(t) is a Heaviside function indicating off and on treatment

Daily viral load since symptom onset for each patient was simulated by running the model with the estimated parameters. The result was used for clustering of the 30 patients, cateogorizing them into 3 groups with different virus decay rate. Then, randomised control trials of antivirals were mimicked by simulations. We assumed that randomization and treatment are initiated with some time lag after symptom onset.

Outcome: Outcome measures from simulations (the duration of virus shedding from symptom onset until the time the virus becomes undetectable, and the area under the curve (AUC) of viral load) were obtained to compute the sample size for different antiviral effects.

Limitations

- A conventional virus dynamics model was used which may not fully reflect the detailed mechanisms of viral dynamics of SARS-CoV-2.
- The mathematical model does not fully encapsulate factors like the immune responses of the participants as the study was conducted on untreated patients.

RESULTS & DISCUSSION

Heterogeneity in Viral Dynamics:

SARS-CoV-2 infected patients were found to exhibit significant variability in viral load decay rates, categorized into three groups: rapid, medium, and slow decay, which could act as confounding factors in observational studies.

Sample Size for Significant Results:

- Detecting antiviral effects (95-99% efficacy) in randomized controlled trials (RCTs) requires over 11,000 participants per group if patients are enrolled without considering treatment timing.
- Early treatment (within 1 day of symptom onset) dramatically reduces the required sample size to approximately 450-580 participants per group.

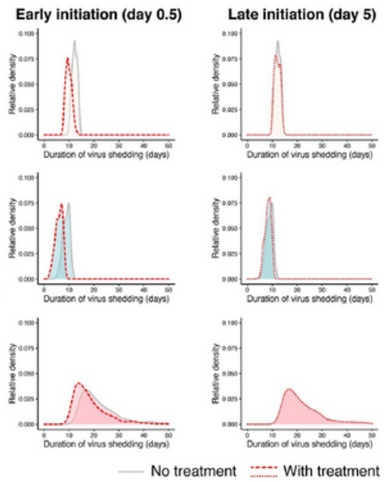


Fig 1. Graphs displaying the relative density distributions of duration of virus shedding since symptom onset for the 3 groups under antiviral treatment with different inhibition rates and different timing of treatment initiation.

Impact of Treatment Timing:

- Early initiation of antiviral therapy results in significant reductions in viral load and duration of virus shedding.
- Delayed treatment (5+ days after symptom onset) has minimal impact on outcomes.

Limitations of Observational Studies

Observational studies often fail to show significant results due to:

- Confounding factors like variability in viral decay rates and immune responses.
- Lack of control over treatment timing.

Practical Recommendations for Trial Design

- RCTs should focus on enrolling patients early (1 day of symptom onset)
- Use viral load reduction or duration of viral shedding as primary outcomes - these are more sensitive to antiviral effects than clinical outcomes like mortality.

CONCLUSION

This study found that estimated association in observational studies was biased largely due to large heterogeneity in viral dynamics among infected individuals, thus making statistically significant effects in randomised control trials difficult to detect with small sample sizes. For future trial designs, the sample size can be dramatically reduced by recruiting patients immediately after developing symptoms, or setting inclusion criteria stratifying subjects by time since symptom onset.

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