Highly-transmissible Variants of SARS-CoV-2 May Be More Susceptible to Drug Therapy Than Wild Type Strains

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Highly-transmissible variants of SARS-CoV-2 may be more susceptible to drug therapy than wild type strains

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Abstract

As of March 2021, no antiviral drug regimen has proved effective against SARS-CoV-2 infection. With the pandemic showing no signs of slowing down, and vaccine campaigns only starting to be rolled out, we appear to have few options other than non-pharmacological measures. Emerging Variants of Concern (VOCs), e.g. B1.1.7, B.1.351, and B.1.1.248, however, are characterized by higher transmissibility (R0).

Here we model and simulate the effect of altered R0 on viral load profiles, and its impact on antiviral therapy. As a hypothetical case study, we simulated treatment with ivermectin 600µg/kg for 3 days initiated at different time points around the infection. Simulated mutations range from 1.25 to 2-fold greater infectivity, but also include putative co-adapted variants with lower transmissibility (0.75-fold).

Antiviral efficacy was correlated with R0, making highly transmissible VOCs more sensitive to antiviral therapy. Viral exposure was reduced by 42% compared to 22% in wild type if treatment was started on inoculation. Less transmissible variants appear less susceptible.

Our findings suggest there may be a role for pre- or post-exposure prophylactic antiviral treatment in areas with presence of highly transmissible variants. Furthermore, clinical trials with borderline efficacious results should consider identifying VOCs and examine their impact in post-hoc analysis.

Introduction

With now more than a year into the COVID-19 pandemic, there have been abundant drug repurposing efforts. Unfortunately, neither established agents (e.g. hydroxychloroquine) nor experimental drugs (e.g. remdesivir) have lived up to their initial promise. In fact, only corticosteroids appear to have limited benefits, and then only on the all-cause mortality and need for mechanical ventilation outcomes in severe cases[1]. As vaccines are being rolled out worldwide, new virus variants are starting to emerge. Most notorious amongst these are the Variant of Concern (VOC) 202012/01 (also known as lineage B.1.1.7), first described in December 2020 in the United Kingdom but in circulation at least since autumn; the VOC 20C/501Y.V2 (lineage B.1.351), discovered in South Africa in the same month; and lineage P.1 (B.1.1.248), described in travelers returning to Japan from Manaus (Amazonas, Brazil) in January 2021[2-4]. A hallmark feature of those VOCs is their high transmissibility, presumably caused by mutations such as N501Y in the spike protein, resulting in greater affinity for the ACE2 receptor[5].

Public health measures like physical distancing, wearing of personal protective equipment, and stay-at-home orders implemented during outbreaks of wild type strains have contributed to reduce overall transmission, but failed, at least partially, to contain the spread of lineages B.1.17, B.1.351, and B.1.1.248. First reports of mutations compromising vaccine efficacy are appearing, causing disruption to national vaccination strategies, and treatment with convalescent plasma may even select for mutations and new variants[6,7]. It is apparent that other preventive measures such as drug-based primary or post-exposure prophylaxis still need to be explored.

Changes in infectiousness may alter intra-host viral dynamics and lead to changes in antiviral drug efficacy. If that is the case, those running clinical trials should account for variants in trial design and analysis. This holds true for completed trials as well, as patients enrolled in the final months of 2020 could have been carriers of the lineages in question.

In this study, we used a recent model of within-host viral dynamics trained on load profiles from Singapore obtained in early 2020, and modified it to simulate the effects of altered within-host infectivity on viral load profiles[8]. To study how these modifications impact on area under the viral load curve (AUC), peak viral load (Ct_{min}), and disease duration, we used a pharmacometric model to simulate treatment with ivermectin (IVM). We selected IVM as it is a drug with well described pharmacokinetics but so far only little documented benefit in SARS-CoV-2 infections[9,10]).

Results

As previously published, viral load dynamics using wild type parameterizations reach positivity ($Ct \geq 35$) after 5.4 d which is maintained for a total duration of 13.5 d, and viral load peaks at 28.4. [8] Compared to wild type strains, increases in within-host R0 resulted in higher peaks (Ct_{min} 25.2-27.4). Positivity is achieved earlier (2.1-3.7 dpi), and, while reduced, durations above the Ct threshold of 35 are similar (11.4-12.7). Total exposure in comparison to wild type profile AUC is increased (AUC 152-402%). Co-adaptation was predicted to result in positivity at 9.1 dpi with a duration of 15.1 d, a peak of Ct_{min} 29.6, and a reduced AUC (66%). Simulated profiles are shown in **Figure 1** and Supplementary Table S1.

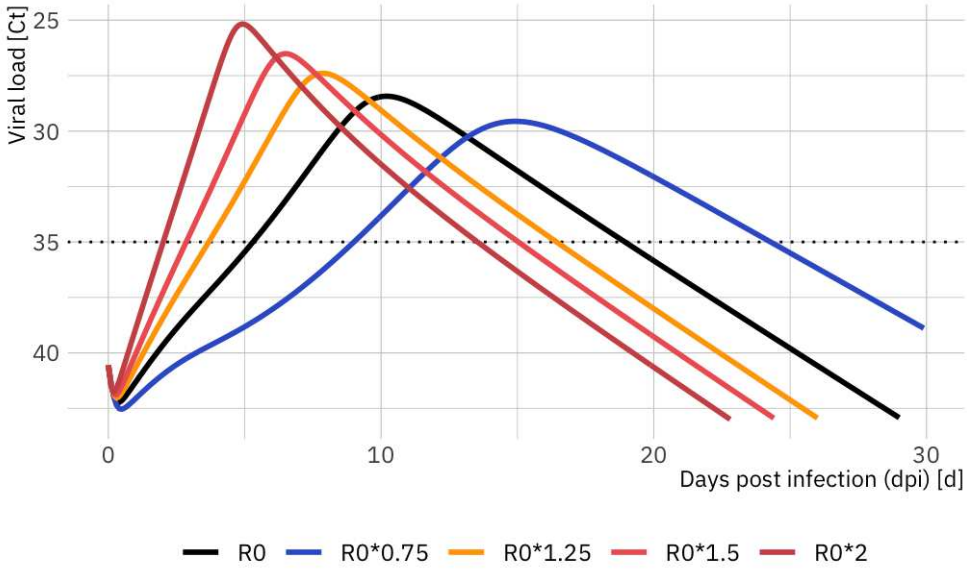

Figure 1 – Simulated viral load profiles by change in within-host infectivity (R0). Black: wild type, blue: less transmissible, orange to red: highly transmissible. Dotted: limit of quantification (Ct 35).

The effects of treatment with ivermectin 600 µg/kg qd for three days were sensitive to R0 as well as timing of treatment initiation relative to inoculation (**Figure 2**). Exposure was reduced the most in highly-transmissible mutations and when treatment started close to the time of inoculation, i.e. 0-2 dpi, where AUCs compared to untreated courses were reduced from 69-70% (R0*1.25) to 58-59% (R0*2). The same intervention in wild type settings was predicted to be 79-80%. Duration was a less sensitive parameter, with a tendency towards prolonged positivity as R0 increases (R0*1.25: 12.1-12.5 vs. 12.5 d untreated, R0*2: 11.5-12.3 vs. 11.4 d untreated). Ct_{min} levels were reduced by up to one log unit in R0*2 (26.2-26.3 vs. 25.2 untreated) while less infective variants showed no susceptibility (R0*1.25: 28.0-28.1 vs. 27.9 untreated, Supplementary Table S2).

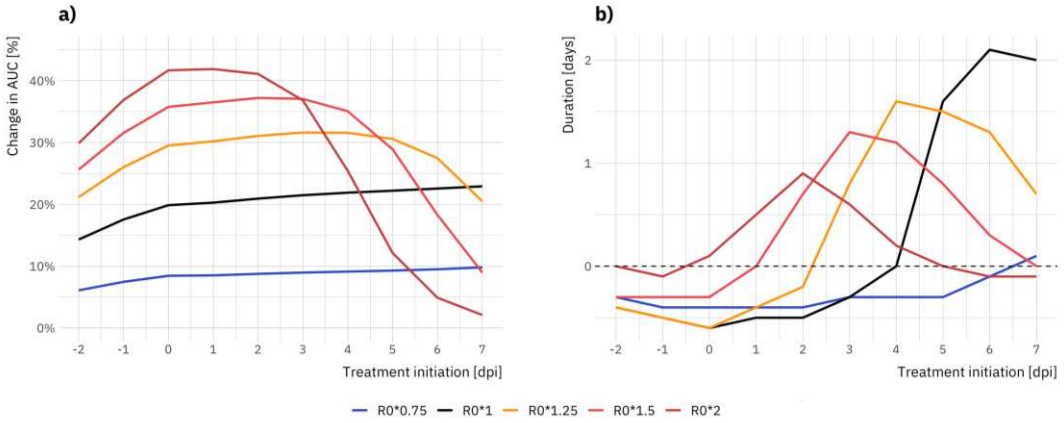

Figure 2 – Changes in total viral exposure as area under the curve (AUC): relative to wild type strain (a) and days above the serological positivity threshold (b). Black: wild type, blue: less transmissible, orange to red: highly transmissible.

Discussion

With this modeling and simulation analysis of emerging SARS-CoV-2 variants, we show the potential influence of altered within-host infectivity on patient viral load dynamics. While the study is not based on *in vivo* data, the results suggest that patients infected with a VOC are likely to experience shorter, stronger exposures to virions, and higher peak loads.

Early treatment of SARS-CoV-2 infections achieved the greatest effect on total exposure and peak load, as previously noted[8,11,12]. Importantly, emerging highly transmissible VOCs appear to be more susceptible to antiviral treatment. The authors would like to stress that ivermectin was used as a placeholder to study the effects on altered within-host infectivity in lieu of other drug repurposing candidates, not as an endorsement for use in patients infected with a VOC esp. while evidence for its clinical efficacy is still emerging[13]. The drug, however, is the subject of ongoing trials which could benefit from our findings, and its pharmacokinetic characteristics are well defined[14].

The expected earlier time to positivity would make it more difficult to base the decision to treat on the availability of diagnostic reports. While it is therefore unlikely that any drug will show satisfactory effects in the practical management of acute cases of COVID-19, there may be a role for selected drugs in supporting non-pharmacological interventions and vaccines as pre- or post-exposure prophylaxis.

It is worth noting that our measures of viral dynamics neither directly translate to clinical courses nor to individual infectiousness, though such correlations have been described[15,16]. We simulated from a model that accounts for acquired immune response as described in mid 2020 in patients from hospitals in Chongqing (near Hubei Province). Immunogenicity of VOCs may differ, as may the response of other populations. Lastly, predicting the effects of prophylaxis is difficult with the type of model employed here as extinction (complete disappearance of virions from the system) is a fringe case.

Given that many trials have included subjects during a time when the now discovered VOCs had already been circulating, it could be worthwhile to revisit borderline efficacious drugs and screen patient samples for these mutant strains in order to perform subgroup analyses, focusing on responders vs. non-responders. This may uncover significant effects against certain variants even when no effect was seen on trial level. If successful, this would open up additional avenues for early treatment or prophylaxis that could complement vaccine campaigns in areas of high VOC prevalence, esp. as long as these are still suffering from production shortages and supply chain problems.

Methods

Viral loads were simulated from a target-cell limited model with acquired immune response around day 10 post inoculation (dpi). In brief, virus particles *V* are considered to infect a pool of target cells *T* with cellular infection rate β. Infected cells *I* shed virions at a production rate p [17]. The rate parameters c and δ determine viral clearance, and cell death of infected cells, respectively. The time-dependent number of target cells (Eq. 1), infected cells (Eq. 2) and circulating virions (Eq. 3) are described by the following system of ordinary differential equations:

$$\frac{dT}{dt} = -(1-\eta)\beta TV \quad (1)$$

$$\frac{dI}{dt} = (1-\eta)\beta TV - \delta I \quad (2)$$

$$\frac{dV}{dt} = (1-\eta)pI - c(1+\varepsilon_{immunity})V \quad (3)$$

where acquired immunity $\varepsilon_{immunity}$ develops according to a sigmoidal E_{max} model, and effects of drug treatment enter dependent on their concentrations and IC_{50} or EC_{50} values for their respective targets (Eq. 4), with *C(t)* being the concentration of the drug at a given time:

$$\eta = \frac{E_{max} \times C(t)}{EC_{50} + C(t)} \quad (4)$$

A detailed description of the model and its implementation are given in Kern et al.[8]

Highly transmissible variants were considered to have 1.25-, 1.5-, and 2-fold increases in the within-host reproductive number R0 (R0 = 3.79) compared to the wild type. Co-adaptation (i.e. a less transmissible mutation) was accounted for by simulating a 0.75-fold decrease in R0. Drug treatments were modeled according to Duthaler et al.[14] The proposed dosing regimen was 600 µg/kg qd for 3d. Simulations were carried out in GNU R (version 3.6.3, R Foundation for Statistical Computing, http://www.R-project.org, Vienna, Austria) and Monolix (version 2019R2, http://www.lixoft.com, Antony, France). Ordinary differential equation (ODE) systems were implemented with the R package deSolve (version 1.28).

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Author contributions

VS: formal analysis, investigation, methodology, software, visualisation, writing - review & editing**;** CK: methodology, software, writing - review & editing**;** CC: validation, funding acquisition, writing - review & editing**;** FH: conceptualisation, formal analysis, funding acquisition, methodology, software, supervision, validation, visualisation, writing - original draft, writing - review & editing**.** All authors contributed to the final version.

Additional Information

Competing interests

The author(s) declare no competing interests.

Data availability

The source code to reproduce the analysis is available on GitHub: https://github.com/cptbern/sars2-variants.

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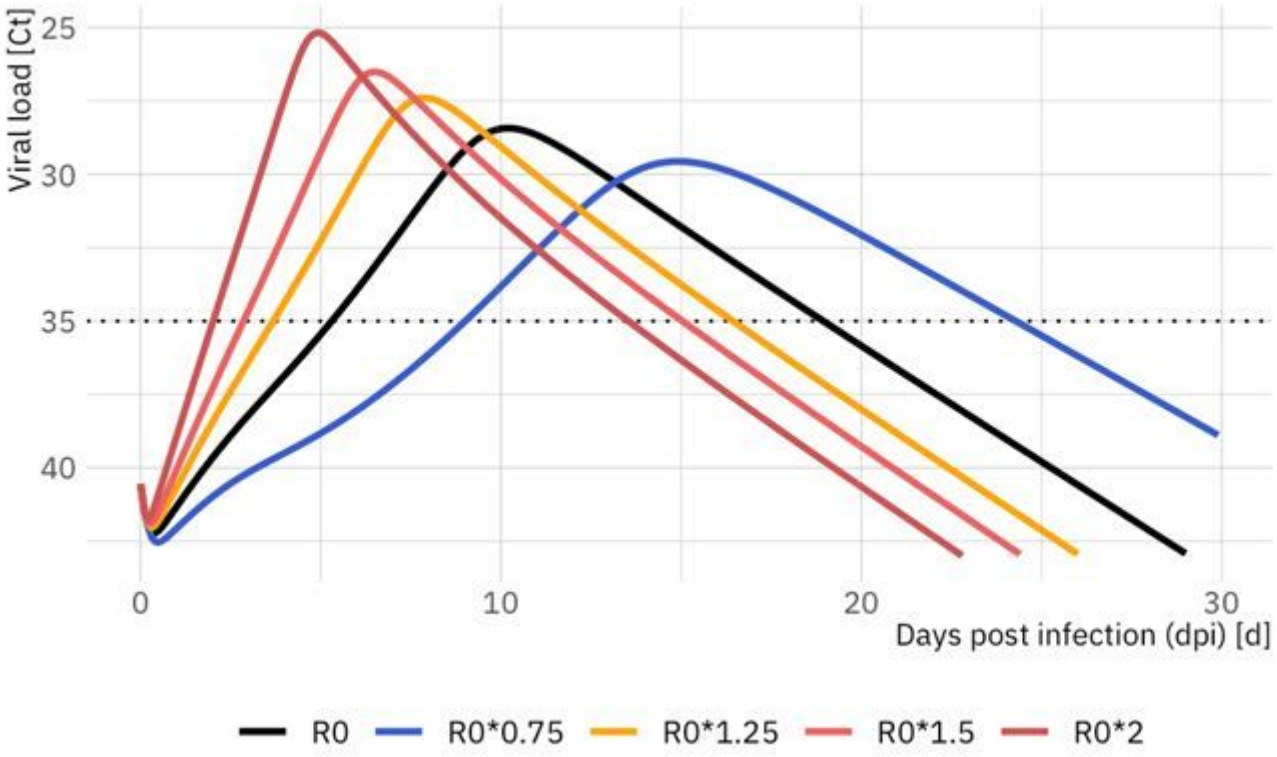
Figures



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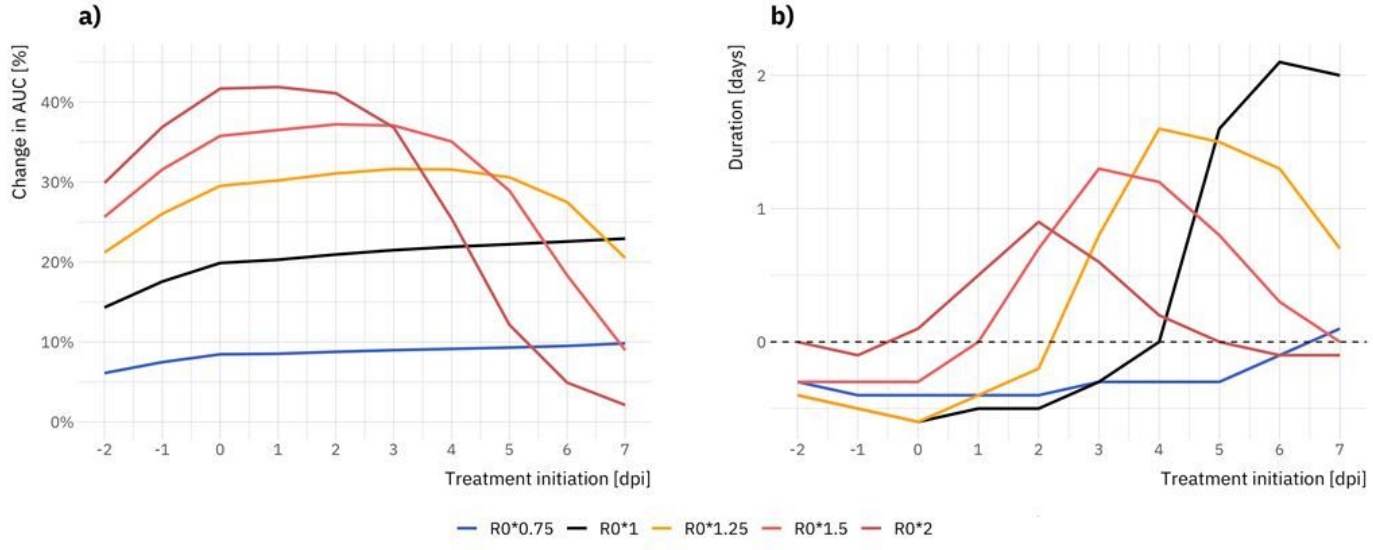

Figure 2

Changes in total viral exposure as area under the curve (AUC): relative to wild type strain (a) and days above the serological positivity threshold (b). Black: wild type, blue: less transmissible, orange to red: highly transmissible.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20210330Sars2variantssupplements.pdf