Review 2: "Predicted success of prophylactic antiviral therapy to block or delay SARS-CoV-2 infection depends on the drug's mechanism of action"

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RR:C19 Evidence Scale rating by reviewer:

Not informative. *The flaws in the data and methods in this study are sufficiently serious that they do not substantially justify the claims made. It is not possible to say whether the results and conclusions would match that of the hypothetical ideal study. The study should not be considered as evidence by decision-makers.*

Review:

Authors propose to use stochastic mathematical modeling to predict the efficiency of prophylactic use of antivirals to prevent SARS-CoV-2 infection and state that it would depend on the drugs mechanism of action. This is a well-written manuscript. However, it is premature for journal publication due to a number of unanswered questions as below:

1) The stochastic modeling proposed has too many assumptions and does not consider many important factors related to the disease mechanisms and epidemiology. Authors claim that this modeling can be used to provide prophylactic therapy for health care workers without going into any specifics on their age, sex, presence of any comorbidities, which are very critical parameters to consider (Communications Biology, 3, 374, 2020; Prehosp. Disaster Med. June 18, 1-4, 2020, Lancet Global Health, 8, E1003-E1017, 2020). For example, the expression levels of ACE2 receptors, the primary target of SARS-CoV-2 spike protein in the epithelial cells, can vary depending on a number of factors.

2) The proposal is assuming that prophylactic/repurposed antivirals for SARS-CoV-2 primarily act by 4-different mechanisms. This assumption narrows the scope of this approach. There are already reports on novel mechanisms of action exhibited by known drugs. For example, TMPRSS2 is a novel target to prevent SARS-CoV-2 attachment to host cells and nafamostat is known to act by this mechanism (Cell 181, 271-280.e8, 2020).

3) Authors do acknowledge that their modeling does not consider the effect of innate and adaptive immune response in individuals during SARS-CoV-2 infection. This again highlights that giving too much emphasis on viral load alone can be misleading. Rather, immune response to viral load in individuals can vary and that can determine

the disease severity, duration and time required for resolution. These factors are not addressed in the modeling proposed which is a major limitation.

4) Authors state that combination therapy would be superior in treating SARS-CoV-2 compared to monotherapy. This is not surprising or new finding, as we have plenty of literature data based on HIV pharmacotherapy, that treatment using drug combinations, using drugs that act by different mechanisms is more efficient than monotherapy.

5) Other criticism is the lack of experimental evidence to support their claims. For example repurposed drugs for SARS-CoV-2 treatment are administered through a wide range of routes (eg: oral, IV, IM or nasal) and have different pharmacokinetic and pharmacodynamics profile. Their dosing frequency needs to be optimized as well for their effectiveness. These parameters should be considered to predict the success of stochastic modeling.

6) The idea and method proposed in this manuscript is not novel and was previously reported by one of authors (Goncalves A ET AL., CPT: Pharmacometrics & Systems, Pharmacology 2020, doi: 10.1002/psp4.12543). Unfortunately, the manuscript doesn't provide any new insights into treating SARS-CoV-2.