Journal	Epidemiologia (https://www.mdpi.com/journal/epidemiologia) (ISSN 2673-3986)
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Title	Modeling the Effects of Drugs of Abuse on Within-host Dynamics of Two HIV Species
Authors	Peter M. Uhl , Naveen K. Vaidya *
Special Issue	Mathematical Modeling for Understanding Viral Infections Within-Host and Between-Host (https://www.mdpi.com/journal/epidemiologia/special_issues/Mathematical_Viral)

Abstract Injection drug use is one of the most significant risk factors associated with contracting human immunodeficiency virus (HIV), and drug users infected with HIV suffer from a higher viral load and rapid pathogenesis. While replication of HIV may result in many mutant viruses that can escape recognition of the host's immune response, the presence of morphine (a drug of abuse) can decrease the viral mutation rate and cellular immune responses. This study develops a mathematical model to study the effects of morphine-altered mutation and cellular immune response on the within-host dynamics of two HIV species, a wild-type and a mutant. Our model predicts that the morphine-altered mutation rate and cellular immune response allow the wild-type virus to outcompete the mutant virus, resulting in a higher set point viral load and lower CD4 count. We also compute the basic reproduction numbers and show that the dominant species is determined by morphine concentration, with the mutant dominating below and the wild-type dominating above a threshold. Furthermore, we identified three biologically relevant equilibria, the infection-free, mutant-only, and coexistence, which are completely characterized by fitness cost of mutation, mutant escape rate, and morphine concentration.

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Does the introduction provide sufficient				

background and include all relevant references?	( )	(x)	( )	( )
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Comments and Suggestions for Authors

Comments (major)

1. The authors over-interpret the results of morphine on virus dynamics. Measuring impact is extremely complicated and stating that all the impacts assumed in the model are "experimentally verified" is a bit naive. Here are specific details:

A) morphine makes T cells more susceptible to SIV/HIV infection. This is not fully established. For example, increasing CCR5 expression does not have to result in higher infection rate - for example, if a T cell expresses 10,000 CCR5 molecules and morphine increases that 2 fold but HIV needs 1,000 molecules for expression, this increase is irrelevant. Original data on CCR5 expression have been overinterpreted by Vaidya et al.
B) the fact that morphine impacts virus evolution is extremely imprecise. Evidence that morphine changes mutation rate of the virus (i.e., ability of RT to make errors when making DNA from RNA) has not been documented and is highly unlikely. There are many other reasons for why SIV may evolve slower in morphine-using monkeys. For example, lower rates of metabolism may result in all rates (T cell division/activation) to be lower, this, showing slower accumulation of mutations.
C) How morphine impacts CTL response is not shown. How would morphine impacts CTL division rate? Is that naive T cell production from thymus? Is it CTL sensitivity to antigen? None of that has been thoroughly tested in experiments. Just a note - to detect a change in only 1 parameter requires a lot of specific experiments which have not been performed.

Authors performed sensitivity analyses but the results are not properly interpreted. Ok, these parameters (XYZ) are "more important". So what? At present, it is pretty much useless unless we understand why these parameters are important, how does it relay to disease, etc.

I will still insist on my interpretation that all answers authors found are logical consequences of the assumptions. Why do we need the model? Precise predictions of this model will strongly depend on parameters which are largely unknown (reference 30 is not a good one because many parameters in that paper have not been rigorously estimated due to limited data, thus, were overfitted).

Minor comments (not sure is these are useful):

"rapid pathogenesis" in abstract is jargon.

abstract: The conclusion that wild type virus outcompetes escape variant contradicts conclusion on 3 steady states listed.

Abstract: Higher set point with WT virus - not because of escape but because of morphine. This is obvious because you make morphine to make monkey more susceptible to SIV

Page 2: "Many mutations due to RT" - this is imprecise. Because mutations occur during infection given RT mutation rate and HIV/SIV genome size, most RNA->DNA conversions are fully correct (you may want to verify this personally!)

Page 2 - "increased CD4+ T cells" - this is jargon.

Page 5 - make sure you are clear which parameters are "estimates" vs. taken. Because none of the parameters in this paper are estimates, these should be listed as "taken from literature".

Why is the virus decline after ART is different in two sets of "monkeys? (Figure 6)

Page 19: 300 count decrease. What does that mean? Is that from 10^6 to 10^6-300 - which is irrelevant then.

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