Reviewer's Responses to Questions  
  
Note: In order to effectively convey your recommendations for improvement to the author(s), and help editors make well-informed and efficient decisions, we ask you to answer the following specific questions about the manuscript and provide additional suggestions where appropriate.<br><br>1. Are the objectives and the rationale of the study clearly stated?<br><br>Please provide suggestions to the author(s) on how to improve the clarity of the objectives and rationale of the study. Please number each suggestion so that author(s) can more easily respond.  
  
Reviewer #1: Yes  
  
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2. If applicable, is the application/theory/method/study reported in sufficient detail to allow for its replicability and/or reproducibility?<br><br>Please provide suggestions to the author(s) on how to improve the replicability/reproducibility of their study. Please number each suggestion so that the author(s) can more easily respond.  
  
Reviewer #1: Mark as appropriate with an X:  
Yes [X] No [] N/A []  
Provide further comments here:  
  
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3. If applicable, are statistical analyses, controls, sampling mechanism, and statistical reporting (e.g., P-values, CIs, effect sizes) appropriate and well described?<br><br>Please clearly indicate if the manuscript requires additional peer review by a statistician. Kindly provide suggestions to the author(s) on how to improve the statistical analyses, controls, sampling mechanism, or statistical reporting. Please number each suggestion so that the author(s) can more easily respond.  
  
Reviewer #1: Mark as appropriate with an X:  
Yes [] No [] N/A [X]  
Provide further comments here:  
  
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4. Could the manuscript benefit from additional tables or figures, or from improving or removing (some of the) existing ones?<br><br>Please provide specific suggestions for improvements, removals, or additions of figures or tables. Please number each suggestion so that author(s) can more easily respond.  
  
Reviewer #1: No  
  
  
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5. If applicable, are the interpretation of results and study conclusions supported by the data?<br><br>Please provide suggestions (if needed) to the author(s) on how to improve, tone down, or expand the study interpretations/conclusions. Please number each suggestion so that the author(s) can more easily respond.  
  
Reviewer #1: Mark as appropriate with an X:  
Yes [X] No [] N/A []  
Provide further comments here:  
  
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6. Have the authors clearly emphasized the strengths of their study/theory/methods/argument?<br><br>Please provide suggestions to the author(s) on how to better emphasize the strengths of their study. Please number each suggestion so that the author(s) can more easily respond.  
  
Reviewer #1: Yes  
  
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7. Have the authors clearly stated the limitations of their study/theory/methods/argument?<br><br>Please list the limitations that the author(s) need to add or emphasize. Please number each limitation so that author(s) can more easily respond.  
  
Reviewer #1: Yes  
  
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8. Does the manuscript structure, flow or writing need improving (e.g., the addition of subheadings, shortening of text, reorganization of sections, or moving details from one section to another)?<br><br>Please provide suggestions to the author(s) on how to improve the manuscript structure and flow. Please number each suggestion so that author(s) can more easily respond.  
  
Reviewer #1: No  
  
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9. Could the manuscript benefit from language editing?  
  
Reviewer #1: No  
  
  
  
Reviewer #1: The manuscript describes a mathematical model that incorporates the effect of morphine on HIV infections. The authors use mathematical analysis, computer simulation, and sensitivity analysis to study the role of morphine in HIV infections. The manuscript is well-written and the analysis is thorough. I have a few minor comments:  
**Comment:** - I don't believe the authors need to change how mutation is incorporated in the model, but they could perhaps discuss/justify the following choices. Why is it assumed that there is a fitness "cost" (0<F<1) for mutations --- sometimes mutations result in a competitive advantage, particularly in the presence of drug treatment. Any thoughts on how a more competitive mutant might change the analysis? Why is there no back-mutation? Mutation in viruses is caused by random changes in the amino acid sequence --- surely it's just as likely to switch one way as it is to switch back?

**Response:** The idea of a fitness cost is related to the immune escape ratio. Our rationale is that the mutant have an advantage over the wild-type by being able to escape from CTLs (the B parameter) and a disadvantage from the fitness cost of escape (F). Allowing for an advantageous fitness cost (which could be modeled as a negative value for F) would make it much more likely that the mutant dominates the wild-type. Back-mutation was not included simply to limit the number of terms in the model, and we have added language to the discussion section addressing these points.

**Comment:** - Units are sometimes italicized, sometimes not. This should be consistent.

**Response:** Units are no longer italicized consistently throughout the manuscript.

**Comment:** - In the second point of the highlights, "outcome" should be "outcompete." 

**Response:** [I don’t think I have the highlights]  
  
  
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