Reviewer's report

**Title:** Modelling imperfect adherence to HIV induction therapy

**Version:** 2  **Date:** 18 June 2009

**Reviewer:** Selwyn Joseph Hurwitz

**Reviewer's report:**

06-17-2009

Second review of manuscript by Rachelle E. Miron and Robert J. Smith.

**General comments:**

The paper is presented in a more balanced manner than the previous version. However, the general tone still appears to be biased in favor of treatment interruptions. As noted in the revised manuscript on page 2 and elsewhere: “Scientific literature cautions patients against taking any holidays while on therapy [23],” during HAART therapy.

This manuscript could be accepted with modification.

**Specific comments**

1. The title “Modeling imperfect adherence to HIV induction therapy”, is suitable.

2. Page 1, the sentence: Can we determine the maximal length of a drug holiday and the number of subsequent doses that must be taken to avoid resistance? Suggestions: Change “must” to “may” or “could”, and “to avoid” to “while still avoiding”.

3. Without further substantiation words like “unrealistic”, “overwhelming” and “relief”, should be replaced by more balanced terminology.

Page 2. “but overwhelming side effects, as well as the inconvenience of following a strict regimen, deter patients from taking their drugs.”

Page 8: “Since there are such a high number of patients who are unable to take their drugs regularly, drug holidays can be a form of relief”.

It should be clarified that not all regimens have “overwhelming” side effects, making compliance less “unrealistic” with some HAART regimens than with others.

“Scientific literature cautions patients against taking any holidays while on therapy but this is unrealistic”.

It would be helpful to supply a reference (preferably a review article), dealing with compliance during induction therapy to substantiate how “unrealistic” compliance is.

There are many assumptions inherent to the model that should be discussed in
the model text:

i. \( s(t) \) is modeled using a version of the Emax model. The more general form to
this relationship is the sigmoidal Emax model in which
\[ s(c) = \frac{R(t)}{R(t) + IC50^\#}, \]
where \( \# \) are superscript of Greek symbol eta.

Thus the underlying assumption in the model used is that efficacy changes with
concentration to a unit power (\( \# = 1 \)). The authors should either provide a
reference to substantiate this assumption, or mention that this assumption was
made.

ii. The pharmacodynamic model assumes that all tissues harboring HIV are
exposed to the same concentration of drug. This is obviously an
oversimplification. e.g., protease inhibitors and many NRTI do not penetrate the
blood brain barrier easily. Also, cells in some tissues contain higher levels of
kinases that phosphorylate NRTI to their active NRTI-TP than others. This should
be mentioned in the text.

iii. The model does not address relative rates of mutation and/or selection of
resistant viruses for the various drugs.

iv. In the case of nucleosides it is the cellular concentration of active nucleotide
(eg., AZT-TP, 3TC-TP, etc), that are responsible for inhibition of viral reverse
transcription. Although this is mentioned in the heading of Table 1, it should also
be described in the model and discussion sections.

5. We suggested in our previous review that it was preferable to base the plasma
concentration versus time profiles on the actual published pharmacokinetics of
the compounds. Impulse differential equations based solely on maximal
concentrations and terminal plasma half-lives could overestimate drug exposure,
unless the terminal phase of the plasma decay curve accounts for the majority of
the period between doses (AUC\#). This should be mentioned in the model
section, and where possible checked to ensure that this was the case for the
various drugs simulated.

6. Theoretical Results Section

Page 5. It is interesting that 3TC and (-)-FTC were listed among the “weakest”
drugs in each cocktail, given that the cellular half-lives of their active
triposphates are among the longest of the drugs described in the text. This
should be discussed in the text.

Figure 2. Graph A could be eliminated, as it does not contain additional
information than Graph B alone. Also, equilibration of drug concentration is
reached within 5 days, so that plotting beyond this time is redundant.

Figure 3. Drug concentrations at equilibrium look identical for regimens A and B.
Therefore, it is only necessary to show one graph and discuss the differences.

Figure 4 through 8: Figures A and B could be combined.
Overall Questionnaire:
1. Is the question posed by the authors well defined? yes
2. Are the methods appropriate and well described? yes
3. Are the data sound? Not applicable
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? yes
5. Are the discussion and conclusions well balanced and adequately supported by the data? See comment section
6. Are limitations of the work clearly stated? See comment section
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? yes
8. Do the title and abstract accurately convey what has been found? yes
9. Is the writing acceptable? yes

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests