Reviewer's report

Title: Modelling imperfect adherence to HIV induction therapy

Version: 3 Date: 30 September 2009

Reviewer: John E Mittler

Reviewer's report:

Given the reviewers were not completely satisfied with the revision, I gave this a “fresh read” this time. The consensus of the previous reviews was that the authors did some things well (e.g., the authors have come up with a nice way of modeling drug concentrations) while other aspects (e.g., clinical-immunological context) were somewhat naïve and/or simplistic. In the course of responding to these criticisms, the authors have improved the manuscript quite a bit. However, the paper could benefit from another round of revisions.

Major compulsory revisions:

1. The authors should consider if the same modeling concepts could be applied to additional treatment scenarios (e.g., booster therapies, the initial year of HAART); that is, other scenarios in which patients might be tempted to take holidays due to a high pill burden. Doing so might broaden the appeal of the paper.

2. While the authors have improved this from the original version, I continue to be somewhat uncomfortable with their attempts to make specific predictions about specific therapies. The authors should go through the manuscript one more time to look for additional places where they could soften specific statements about specific drugs. At the bottom of page 11, for example, the authors should consider replacing “triple-drug cocktail FTC/TDF/EFV can have a 6 day” with “an FTC/TDF/EFV-like triple-drug cocktail can have a 6 day.”

Minor compulsory revisions:

Page 2: “However, PI-sparing…” Consider changing “However,” to “Recently,”

Page 3, line 1: “new” -- Induction therapy has been attempted on and off and on again since the mid-late 1990’s.

Page 3, bottom of first paragraph: Change “two RTIs and a PI” to “two RTI-like and one PI-like drugs.” (ditto page 15).

Page 11, “prescribed tolerance of perfect adherence” -- Please define what you mean by “prescribed tolerance” in the methods (or right there in the same sentence).

Figures 4-10: The patterns are similar. I think these could be collapsed into one or two figures.
Figure 11: This is the more important figure. I think the paper would be more compelling if the authors expanded this type of analysis (at the expense of Figs 4-10).

Page 16, Last paragraph. Would be nice to end with a more carefully tailored final message. Please define what you mean by second-line. For the last sentence, I suggest changing this to a relative statement so that naïve readers don’t inappropriately conclude that FOTO is superior to continuous therapy. For example, that FOTO is superior to “30-days on, 7-days off” (or whatever). Alternatively fuse to the previous sentence. Briefly explain (3-4 words may suffice) why not including ZDV, d4T, and DLV is important.

Legend to Figure 3, “dashed line”: I only saw a red line. While I am on the subject, some more detail on where this came from would be helpful.

Table 2: In response to my previous set of comments, the authors have clarified that the results in Table 1 are “theoretical.” The same qualifications need to be added to Table 2.

Discretionary revisions:

Abstract: The rationale for modeling interruptions during induction therapy are improved from the original submission. Word limits permitting, I suggest repeating the motivation in background of the abstract.

Page 3, second paragraph from the bottom: Consider adding some more detail about the model’s simplifying assumptions after the first sentence.

Page 4: The equations would be a lot easier to follow if the authors used mnemonic symbols. Consider changing subscript Y to subscript M (for mutants), changing d_s to d_L (for latent cells), r_r to r_s (for sensitive), and r_Q to r_R (for resistant).

Page 5, after definition of theta: Briefly mention your conservative uses of R1 and R2.

Page 7, second paragraph “dynamics are not” -- sentence has confusing double negative.

Page 11, “number of missable and subsequent doses” -- Add a brief reminder of how this is defined (e.g., “as defined by equations xxx and yyy”, where xxx and yyy are new equation numbers added to section 3.1).

Page 12, “We considered an extinction threshold…” Consider moving this information up front (methods section or the beginning of the simulations).

Table 1: Add standard deviations where available. For the data under columns R1 and R2 two or three digits in the exponent should be sufficient.

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.