Reviewer’s report

**Title:** The effect of imperfect adherence on HIV induction therapy: how many drug holidays can you take and how long should they be?

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**Reviewer:** John E Mittler

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Comments on Miron and Smith “The effect of imperfect adherence on…”:

The authors use a set of impulsive differential equations to model the effects of “drug holidays” on the dynamics of drug resistant viruses. The model includes target cells and free viruses and cells infected with wildtype and resistant viruses, as well as cells that have absorbed drugs that levels that inhibit wild type and/or resistant viruses. The authors use the model to predict the number and length of drug holidays under which resistant virus will be suppressed for specific combinations of drugs.

The paper addresses an important problem that can be addressed using mathematical models. The equations are well formulated mathematically and address the complexities of resistance in a simplified, though appealing, way. That said, the study has several limitations, including inadequate descriptions and justifications of some their modeling strategies, neglect of some key biology, and an incautious presentation of results concerning particular treatment regimens (summarized below under major revisions). Despite their apparently conservative assumption of modeling monotherapy, I will need more convincing that their conclusions are as conservative as they stated.

Major compulsory revisions

1. Tables 1 and 2: While specialists in the field will understand this study for what it is (results from a conceptual model), the authors need to be cognizant that some HIV patients could take the results in tables 1 and 2 literally. My fear is that an unsophisticated patient taking a d4T-3TC-NVP regimen, for example, might use this as justification for taking up to 45 2-day drug holidays--a strategy that is not supported by real data. The authors need to be very careful to alter their readers to the fact that these are extrapolations from a mathematical model that has not been tested in the clinic. Keywords altering readers to this caveat should be given in both the text and the table legends.

2. Discussions about Table 1 in the text: Further discussions about the actual increase in resistance imposed by single mutations to particular drugs and the qualitative effects of allowing for double mutations could inform readers as to whether the number of missable doses calculated in this table is as conservative as stated.
3. Introduction: The overall strategy of the paper could be spelled out better. Intuitively, I would expect that drug holidays would be more dangerous during the maintenance phase (when patients are treated with fewer drugs) than during the induction phase (when patients are treated with more drugs); however, the authors focus their analyses on drug holidays taken during the induction phase. I suppose that modeling the effects of drug holidays during the induction phase could be justified, however, if the induction therapy is especially intense (e.g., four drug induction) and the idea is that patient wants to take some holidays during an extremely intense induction phase. Whatever they choose, the key thing is to be clear about the scenarios they are trying to model.

4. Results: The authors should comment on the threshold for extinction of the mutant virus. The point of induction-maintenance therapy is that viruses resistant to the maintenance therapy drop to zero during the induction phase. The current model allows for non-zero fractional concentrations of resistant virus. In Figures 3B and 3D, for example, the concentration of resistant virus hovers around $10^{-20}$, a value that is far below the concentration at which virus falls below 1 per body.

5. A set of summary figures that summarized the outcomes from numerous simulations of the sort shown in Figures 4 and 5 could be useful. Again, the key thing, I think, is to show the combination of parameters/conditions under which resistant virus is likely to be extinct (the primary condition for IM therapy to work).

6. The authors should point out that recent trials of structured treatment interruptions (STIs) showed that therapy interruptions actually increase toxicity events. See, for example, references to the SMART trial, which should be referenced along with other recent STI trials. (BTW: The failure of STIs to decrease toxicities was a huge surprise to the HIV/AIDS patient and treatment communities. The reasons for this are not completely understood.)

7. Page 6, “Here, the effects of taking more than one drug holiday allow patient the freedom of safely extending these holidays by providing them with calculated restrictions.”: An example of statement that needs to be revised to more cautiously reflect uncertainty in the modeling.

Minor essential revisions

Appendix: The model does not consider latently infected cells. A potential problem with structured treatment interruptions (STIs) not considered here is that transient increases in the number of resistant viruses could result in the buildup of a pool of cells latently infected with resistant virus. The authors should briefly discuss this point.

Page 4, “that the average drug concentration be within the range of the impulsive orbit.”: The logic wasn’t clear to me. I think it would be worthwhile expanding on this point in the text of this paper. Also, the authors need to define the term impulsive orbit and clarify whether average refers to the arithmetic or the geometric mean.
Page 5, “Curlin et al. (2007) show that a 180-day induction phase was ideal…” While 180 days is a reasonable summary of their results, Curlin et al.’s simulations actually yield a range depending on values of unknown parameters. Consider softening to say that “…show that an induction phase on the order of 180 days was ideal…”

Tables 1 and 2: The authors also need to caution their readers that pharmacokinetic parameters can vary from patient to patient. Tables 1: Please provide references for the values in this table.

Figure 4: A confusing figure. The first thing, I think, would be to establish what happens if there are no holidays before modeling the effect of departing from the described holiday regimens “described in this paper.” (Keeping in mind that taking drug holidays is itself controversial for the reasons given above). The figure also suffers from being very crowded. The authors’ use of small fonts and difference scales for resistant virus made it hard to interpret the results at a glance. I recommend graphing the data on a log scale.

Major (discretionary) advice

I strongly advise the authors to consult with some HIV/AIDS clinicians before resubmitting this paper. I keep thinking that there may be some way of simplifying the presentation that will make the paper appealing to mathematically inclined readers without offending clinicians.

Discretionary revisions

Page 4, “a prescribed tolerance of perfect adherence”: The terms “tolerance” and “prescribed tolerance” need to be defined from the outset.

Figures 1, 4, and 5: The fonts and line quality are poor compared to Figure 2.

Page 7, use of I for wildtype, Y for mutant: (Optional) Consider use of mnemonic symbols. For example, subscript-M for mutant.

Table 1, Values for R1 and R2: (Optional) Use of powers of 10 would be more readable than powers of e.

Figure 3: This figure is confusing. It was not clear to me how the shape of these curves relates to tolerances listed in the legend. I noticed 12 spikes in panel A but only 9 spikes in panel B. How does this relate to the tolerances? The origins of the blue regions are not clearly explained. It took me a couple of readings to realize the blue regions are really a smear. I think it would help if they simulated for less time and stretched the figures out. For this figure and the next, it would also be helpful to plot dots or lines representing times when patient is on therapy vs taking a drug holiday.

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.