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: Robert Stengel

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It's clear that the authors have done some interesting research, but that work could be explained more clearly. As I read from the beginning, here are my comments and questions.

The Abstract should have a brief concluding sentence. It is left hanging, describing work done but not what it shows.

Clinical trials have shown that interrupted therapy generally results in more aggressive disease. What brings you to the conclusion that the drug holiday alternatives presented here are realistic? Can you be sure that your models have captured the biology well enough to contradict the clinical evidence?

You describe induction-maintenance (IM) strategies that are consistent with the “hit hard, hit early” therapy proposed by Ho and colleagues more than a decade ago, and various studies of “optimal” therapy support the same conclusion. The IM description on p. 2 defines the induction phase as a period of intensified dosage and the maintenance phase as a long-term period at lower dosage. However, the last sentence of the 2nd full paragraph suggests that I and M phases might overlap; taken literally, that would mean even higher dosage than the induction level during the overlap period. Is that what you mean?

The interplay between the HIV/T-cell dynamics, modeled by ODEs, and the pharmacokinetics of the drug uptake, modeled by “impulsive” differential equations is not clear. Although the effects of various drug regimens on viral load are shown in Fig. 4 and 5, it seems that the bulk of the paper addresses just the pharmacokinetic aspects of the problem.

“Impulsive” differential equations are seen to be simply linear ODEs that are uncoupled from the immune-response dynamics and are re-initialized each time a drug dose is given. The discontinuous change in the state element is, of course, not physically possible, although it could be a reasonable assumption in some circumstances.

This added complexity could have been avoided and a better representation of dosage effects could have been obtained if the pharmacokinetic effects had been modeled as simple ODEs with an impulsive input (preferably with finite magnitude over a brief interval of time; the area of the impulse represents the actual dosage of the drug) when the dose was given. This introduces the lag in
initial uptake of the drug as well as the decay in internal concentration that occurs over time, a much better model of the drug’s concentration. Furthermore, it allows for the distinction between the chemical composition of the drug as given (e.g., \( u \)) and of its internalized form (e.g., \( R \)), which could be affected by digestion, absorption, transport to active sites, and so on.

Figure 1 purports to portray the “dynamics of drugs”, yet there is no time or frequency variable in the figure. What does it mean for a drug level to be sufficient to control the virus? Are these steady-state values? It is my understanding that no drug regimen is capable of maintaining HIV stasis indefinitely. While the figure is conceptually appealing, the meaning and rigor of the vertical-axis variable is unclear.

What is a “10-fold mutant strain?”

Section 3 indicates that the authors have investigated many alternative drug strategies, but what they actually did and what results they obtained are unclear. Section 3.1 discusses “missable and subsequent doses” but barely hints at how conclusions were reached. It does not present a solid base for understanding the methods and numerical results of the next section. Reference is made to doses missed in the induction phase or the maintenance phase, numbers of acceptable or unacceptable misses are floated without support, and levels of tolerance are thrown into the mix. The section is neither well-organized nor substantive.

Numerical simulation is discussed in Section 3.2, but the treatment is entirely random. Obviously, a lot of simulations were run, but once again, the description of methods, the orderly comparison of alternatives, and the structure of describing results is inadequate.

Section 4 describes results that are not shown and suffers from the problems mentioned above.

The model is adequately, but not satisfactorily, presented in Appendix A. My guess is that if it had been incorporated in the body of the text, some of the previously mentioned difficulties would have been avoided. While I understand the differences in convention for biology papers and those published in the physical, mathematical, and engineering sciences, this paper goes too far in hiding its mathematical underpinnings.

Appendix B seems to confirm my earlier comment that the paper is primarily about pharmacokinetics, as it is called “Mathematical Analysis” and is directed solely at dosage dynamics. The sequence of equations is entirely too long. It would be far better to define a state transition matrix (a scalar for the single-drug case) and note that the propagation of \( R \) is recursive. The appendix could be reduced from 4 pages to one if properly written and motivated in the body of the text.

Overall, this is an important topic, the authors have developed keen insights about the problem, have done a lot of supporting calculations, and have prepared a manuscript. Now, they must take a long, hard look at how best to share their
knowledge with the public. They must re-write the paper to give the subject its due.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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