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: Selwyn Joseph Hurwitz

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“The effect of imperfect adherence on HIV induction therapy: how many drug holidays can you take and how long should they be?” Rachelle E. Miron and Robert J. Smith?

Overall review:

This is an interesting mathematical approach for examining the potential flexibility of drug treatment regimens in general. This approach may be useful for evaluating the effect of dose interruptions in drug regimens, provided that pertinent aspects of a particular drug and disease are incorporated into the model. However, this model seems simplistic, and could lead to overly optimistic conclusions with regard to the flexibility of HIV regimens. This paper could be considered for publication with major revisions.

Major Compulsory Revisions


2. The underlying assumption in the model was that plasma concentrations are a direct measure of drug efficacy. This assumption may hold for protease inhibitors and non-nucleoside reverse transcription inhibitors, in which the parent compound is responsible for viral inhibition, but not for nucleoside reverse transcription inhibitors (NRTI), which are prodrugs.

3. ABC, ddI, FTC, 3TC, d4T, TDF, and ZDV, are NRTI. The antiviral potency of NRTI is related to the accumulation of the active NRTI triphosphate (NRTI-TP), which competes with natural nucleoside triphosphate (NTP) for the viral reverse transcriptase (RT), and/or produces chain termination, once incorporated into the replicating viral genome. The cellular half-life of the NRTI-TP may be quite different compared with the NRTI in plasma. For instance, the half-life of 3TC and (-)-FTC is about 5-7 h and 8-10 h in plasma, respectively, while the half-lives of cellular 3TC-TP and FTC-TP are 15-16 h and 29-56 h, respectively. Similarly, for tenofovir, the plasma half-life is 12-17 h, while cellular half-life of the active cellular diphosphate is > 60 h. Also, cellular NRTI-TP levels are not always
proportional to plasma levels, due to inter-individual variance in cellular kinase levels, and proportion of activated CD4+ cells for cell cycle dependent thymidine NRTI, AZT and stavudine. The model should be revised to make it suitable for NRTI. Alternatively, the existing model may be more suitable for protease inhibitors, fusion inhibitors, of integrase inhibitors, which do not have as complex pharmacodynamic mechanisms of action.

4. An extensive list of equations was provided for the simulations. However, parameter values, with accompanying references were not reported.

5. The model approximated plasma concentration versus time (pharmacokinetics), using impulsive differential equations, and did not consider inter-individual variances in pharmacokinetic. More detailed pharmacokinetic models should have been considered.

6. The model assumes that the CD4+ pool of lymphocytes in blood is the only significant source of HIV infection, and that maintaining drug concentrations at clinical levels result in maximal control of virus replication and control the emergence of resistant virus in all tissues. However, not all HIV susceptible tissues are equally susceptible to existing drugs. For example, lymphoid cells in the GUT are not completely suppressed, even during induction and ongoing HAART therapy (e.g., Chun, TW, et al., J Infect Dis, 2008, and Dandekar, S., Curr HIV/AIDS Rep. 2007). The consequence of these and other viral reservoirs should also be considered or at least discussed in the context of “drug holidays”.

**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'