Reviewer’s report

Title: Immune control of HIV-1 infection after therapy interruption: immediate versus deferred antiretroviral therapy

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Reviewer: Radjin Steingrover

Reviewer’s report:

1) In general:
Paci et al have written an interesting paper describing the results of a computer model that predicts the optimal time of initiation of HAART. Although not stated clearly in the introduction, the study concerns the initiation of HAART during primary HIV infection. The structure of the abstract and manuscript lacks a section describing the goals and objectives for this study. The pages are numbered but the lines are not. A cohort of patients with primary HIV infection is used to provide data for the primary infection group. It’s unclear where the data comes from in the ‘late’ HAART group, as well as the ‘cohort data’ mentioned on page 4. The structure Is actually background-results-discussion-conclusion-methods, lacking is an objectives section indicating the purpose of this work. (minor)

2) Page 2
Background: asymptomatic patients are mentioned. Authors must state clearly if they mean asymptomatic acute HI infection or asymptomatic chronic infection. (minor)

3) Page 3
Background: immediate therapy: can mean initiation of HAART after a maximum of 12 months after infection (the 6 months seroconversion interval + the maximum 6 month therapy initiation delay). Table 1 gives days before therapy, but it’s not clear what it means. (minor)

4) Page 4
Authors describe how simulated data compares to ‘cohort data’ after treatment interruption. Since the results from cohort data are so diverse, authors should provide references to the data they used. If they used only one small cohort, I wonder why they did not test the external validity and robustness of the model against other larger cohorts (published or presented by Desquilbet, Steingrover, Koegl). By selecting only one small cohort as the basis for the model, the choice of this cohort influences the model greatly. Same goes for the data of deferred treatment strategies described on page 5. (major)

5) Page 6
Life long treatment from primary infection is a feasible option in patients that need it. Such was not tested in this study and hence not proven impossible.
Authors may wish to remove or modify this statement. (minor)

6) Page 7

CTL responses are related to viremia, it's not clear however who’s in control (Jansen/Miedema). Authors model rebound of viremia to similar levels in the groups and assume different CTL responses without any validation of this outcome. Viral rebound dynamics are very different in patients undergoing STI after early or deferred HAART (Steingrover/Pogány et al, AIDS) and rather contradictory to the results from the model in this study. This makes one wonder about the robustness of the model. (major)

7) Page 8

Authors conclude that early therapy and subsequent STI leaves the viral rebound undisturbed. No argument is made why the results from the model is so different from multiple studies (Steingrover CROI 2007, Koegl CROI 2007, Steingrover et al AIDS, Steingrover CROI 2008). Also, authors conclude that the study should impact the current treatment strategies currently under study in randomized trials like Primo-SHM and Spartac. The undertaking of these trials shows how the need for robust data is felt in the field. Nonetheless, the authors imply that primary HIV infection needs not to be treated based on the results from the model. (major)

8) Page 9

Predictive of the viral rebound is HIV-1 DNA intracellular concentrations (Yerly et al). Also predictive of the HIV-1 RNA concentration in plasma are genetic factors of the host. Neither is incorporated in the model. Author need to discuss why this results in an acceptable model. External validation needs to show that such a model is indeed capable of producing robust predictions. (major)

9) Concluding remarks

This paper is an interesting effort to model complex data. The model is internally validated based on a small cohort of patients with primary HIV infection undergoing early therapy. The outcomes involve both patients that undergo early and deferred therapy. The outcomes are contradictory to existing study data that is published and presented. An external validation of the model and it’s results is needed before any conclusions can be drawn regarding the treatment of primary HIV infection. The authors may consider other predictors of the dynamics of viral rebound to be added to the model to produce improved results. The authors may want to think and explain about the purpose of the model and its results.

Level of interest: An article of limited interest

Quality of written English: Acceptable

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

Declaration of competing interests: