Reviewer's report

Title: Transient detectable viremia and the risk of viral rebound in patients from the Swiss HIV Cohort Stud

Version: 2
Date: 4 July 2015

Reviewer: David Hanna

Reviewer's report:

This is a well-written study examining the association between virologic blips and viral rebound among 4,094 participants in the Swiss HIV Cohort Study who achieve virologic suppression assessed through more sensitive HIV RNA assays than those initially used to define blip thresholds. The authors found that the risk of viral rebound increased as the blip “magnitude” (in copies/mL) increased, with suggestive evidence of higher risk even at thresholds lower than 500 copies/mL (a current conventional threshold based on Grennan et al.). They also used available data on treatment adherence to conclude that blips may be more likely to be attributed to temporary non-adherence than to random variation in residual viral replication.

The authors are to be commended for their work in a highly clinically relevant but understudied area. They also use rigorous statistical methods to model viral rebound, opting for a parametric survival model optimized for interval-censored data rather than the more conventional Cox regression models. The main (minor) weakness of this paper is that it relies on viral rebound as the outcome of interest; it is unclear whether the lower magnitude blips as measured in this study will result in poor clinical outcomes as a result of viral rebound (although evidence from other studies suggests this). Nonetheless, it is an important contribution to the literature as viral assays continue to improve and become more sensitive.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached): None

Minor Essential Revisions:

1. Abstract: The thresholds used to define “blip” and “viral rebound” should be included in the Methods for clarification.

2. Abstract: The time frame for the study is not presented but should be included. Otherwise, the reader does not know what “newer” is in relation to. This should also be included in either the Introduction or Methods of the main text, as it is never clearly stated.

3. Introduction, line 61: The authors note early studies but the actual studies are not cited. Please include references for these studies.
4. Introduction, line 63-64: It would be useful to note the lower detection limit for the Roche Amplicor assays here, in order to understand the justification for the current study.

5. It would be helpful to include a clearer justification for why there are separate analyses for first and subsequent episodes of viral suppression, perhaps in the Methods section. Also, it should be more clearly described that the “subsequent” episodes are episodes occurring after viral rebound.

6. Results, lines 178-179: Description of alternate definition for viral rebound should first be introduced in the Methods section.

7. Results, line 189: Authors should clarify what comparisons are being made with the two hazard ratios.

8. I would be curious to know what the HR is for continuous blip threshold using the standard Cox model. Perhaps this could be included as part of Table 2 (along with the Weibull result).

9. Table 2: Why is CD4 cell count not part of the standard Cox model, and similarly why is # RNA tests per year not part of the Weibull model? A footnote should be helpful to explain this.

10. Appendix A: The last sentence of the Methods section states that “we cannot fit [Model 4, Weibull model] to data from both first and subsequent suppression episodes”. Since this is assumed to be the primary model used for the paper, this sentence should be clarified.

Discretionary Revisions:

1. Abstract: The authors may want to consider describing the assays considered in this analysis as “more sensitive” instead of “newer”, since the former is the actual characteristic affecting measurement.

2. Abstract: If there is room, it would be helpful to include the findings (or at least the P-value for trend) from the model with continuous blip magnitude, in order to be convinced that there is not a threshold effect at 500 copies/mL but rather a continuous/linear effect of blip magnitude on viral rebound (as suggested in the Conclusions). The Conclusion suggests that blips above 200 copies/mL may result in viral rebound, but the data in the Results section do not exactly support this.

3. Introduction, line 74: Should define what “blip magnitude” here means, as it is unclear. It could refer either to HIV RNA level used to define the blip, or the number of blips.

4. Methods, line 103: Here, “size” is used instead of “magnitude”. Should use consistent terminology.

5. Discussion, line 242: The word “these” might be changed to “our” to clarify that the authors are referring to the present study, not the cited studies.
6. Figures 1 and 2: What is the justification for use of 125, 350, and 750 copies/mL for the survival curves of blip magnitude per 100 copies? It seems that survival curves for 100, 200, 300, 400, etc. would be more intuitive for the reader.

7. Figure 2: For curves among non-adherent patients, why not show individual curves per copies/mL to provide more graphical evidence that the probability of continued suppression is independent of blip magnitude?

8. Tables A2 and A3: I would recommend listing all of the covariates in the model in the footnote instead of referring the reader to Table 2.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.