Author's response to reviews

**Title:** Trends in CD4 counts in HIV-infected patients with HIV viral load monitoring while on combination antiretroviral treatment: results from The TREAT Asia HIV Observational Database

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Trends in CD4 counts in HIV-infected patients with HIV viral load monitoring while on combination antiretroviral treatment: results from The TREAT Asia HIV Observational Database

Dear Editor,

We would like to re-submit the revised manuscript of the above titled article to BMC Infectious Disease.

We would like to thank both referees for their careful review and helpful suggestions. The following pages list point-by-point responses to the comments of the referees and the editorial requests.

All the authors have seen and approved the manuscript and have contributed significantly to the work. The manuscript has not been published and is not being considered for publication elsewhere.

We look forward to your reply.

Yours sincerely,

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Response to the referees’ comment

Referee 1:

Major comments
1. My main concern is about the model. Baseline CD4 and baseline HIV VL were not tested for their effect on CD4 slope. HIV viral load was only considered by a linear increase but no distinction was performed between undetectable viral load (VL<=500) or higher viral load. Did you test any interaction with time, such as HIV viral load and time. Last, compared to patients with CDC stage A, patients with TB and/or ADI, and patients with non-TB ADI, presented a greater gain of CD4. However this striking result was not discussed.

Our response:
The increasing in CD4 slope after TB and or other non-TB diagnosis, compared to patients with CDC stage A illnesses, we thought might be simply due to the increased total lymphocytes during active infections. The increase could also be the short-term response due to the increased adherence to cART and introduction of treatment for TB or other ADI. This has been included in the Discussion section (page 8, paragraph 2)

In the multivariate model, we fitted both CD4 count and HIV VL as time-dependent variables. The binary HIV VL variable (above or below 500) was not statistically significant when included in the model. We did not include CD4 count and HIV VL at baseline for the following three reasons: first, a large proportion of patients did not have the tests at treatment initiation (approximately 25% of patients had no CD4 count and 45% HIV VL, Table 1); second, the model aimed to help clinicians in this region to assess the status of immune system with the clinical information at hand (e.g., age, hepatitis status, current CD4 count, time since treatment initiation, etc) where the baseline information on CD4 count and HIV VL may not be readily available; and third, when we included baseline CD4 and HIV VL in a sensitivity analyses based on the subset of patients with baseline data available, the results remained comparable with the model without the baseline CD4 count and HIV VL. We have made these points clearer in the Methods section (page 5, paragraph 1).

2. The description of the patients included could be completed. Years of inclusion should be given, as well as additional information on initial treatment prescribed, treatment switch, and treatment interruption. After 6 months on cART, how many patients achieved virological success, how many ultimately presented virological failure, how many patients died, or were lost to follow-up.

Our response:
We provided additional information on patient recruitment in Methods section (page 4, paragraph 1). We also provided information on follow-up status, survival, initial treatment, treatment change and virological suppression in Results section (page 6, paragraph 1 and 3)

3. Table 1. All patients included were naïve but 11% had HIV viral load <500 copies/ml at cART initiation. This number seems large.

Our response:
We rechecked the data and that is what was reported. The proportion was shown among patients with HIV viral load tests. As shown in Table 1, approximately half of patients did not have a HIV viral test at treatment initiation.
4. Table 2. Disease stage has been categorized as: no AIDS-defining infection; tuberculosis and/or other ADI; non-TB ADI. I do not understand the distinction between the two last categories. It is also not clear if disease stage represented clinical event at cART initiation or at the time of concurrent measurement of CD4 and viral load.

Our response:
The disease stage was revised to “no AIDS-defining infection”, “tuberculosis, with or without other ADI”, and “Other non-TB ADI”. The disease stage was fitted in the model as a time-dependent variable, i.e. at the time of concurrent measurement of CD4 and viral load. This was explained in the Methods section (page 5, paragraph 1) and updated in Results section (page 6, last paragraph).

5. Table 4. Sensitivity analysis was performed restricting the observations to those measured during initial treatment, before any class change or stop for more than 30 days. I am surprised that the number of patients (n=1353) in this sensitivity analysis was also diminished compared to the initial analysis (n=1676).

Our response:
We re-checked the sensitivity analyses, the number of patients included was correct. The endpoint of this study, the CD4 slope, was generated using three consecutive CD4 tests. The patients that were excluded had only three CD4 tests, however, one or more of the CD4 test results fell after the time when there was a class change or stop, consequently, that CD4 slope (and the patient) was not included in the analysis.

6. Discussion page 9. You stated that "(your) data showed a two-phase CD4 count response with a high CD4 count slope in the first six months after treatment initiation followed by a lower slope", but these results have not been displayed since "CD4 slopes were calculated from CD4 counts measured 6 months after cART initiation".

Our response:
In Methods and Discussion sections (page 4, last paragraph and page 9, paragraph 2), we have showed the two-phase CD4 count response (179 vs. 44 cells/µL per year, p<0.001), which is consistent with the literature. In the Discussion section, we suggested that after cART initiation, CD4 counts continued to increase even when the concurrent HIV VL was detectable. However, HIV VL needed to be controlled at a lower level to maintain a positive CD4 count slope when cART continues at later stages, particularly from 6 months to more than 24 months after cART initiation (page 8, paragraph 1).
Referee 2:

Major comment:
1. The ability of ART to cause CD4 gain - also in patients without complete viral suppression - has been the focus of several analyses previously. The list of references included in the current version does not include the most recent publication by Mocroft et al in Antiviral therapy. That paper suggested that the CD4 slope was affected by which drugs were used (PI > NNRTI; non-ZDV > ZDV). Suggest that the authors carefully review that paper and consider including additional variables in their multivariable models.

Our response:
We think it is a very good point to consider drug class and individual drugs suggested by the reviewer. We included drug class and abacavir as suggested by the paper (Table 2), however, none of them remained significant in our final model. We thought this might be due to three reasons: first, the paper by Mocroft et al analysed data from EuroSIDA where the predominant cART regimen was PI-based (46% non-boosted, 23% boosted PI). TAHOD recruits patients from the Asia Pacific region, with NNRTI-based regimen as the most common initial cART (63%, 15% non-boosted and 20% boosted PI). In addition, abacavir was not frequently used in TAHOD; second, the patients who received PI- or NNRTI-based cART as initial regimen might be different between EuroSIDA and TAHOD, which could result in a different recovery pattern of the immune system; three, as suggested by Mocroft et al, larger studies with increased power are needed. Nonetheless, our study provided complementary evidence in patients from Asia Pacific region that CD4 counts continues to increase even when the concurrent HIV VL was detectable. This was included in the Introduction (page 3, paragraph 2), Methods (page 5, paragraph 1), Results (page 6, last paragraph) and Discussion (page 9, paragraph 2).

2. The clinical implications of the findings are not sufficiently discussed in the present paper in my opinion. WHO used previously a viral load of >10,000 copies/mL as indication to switch, but it is generally agreed that if one does do viral load monitoring, when switches should be done more quickly after time of viral failure. Was the time from viral failure an independent determinant of CD4 slope? If one is solely using CD4 cells for monitoring, then this paper is in line with others underlying that indeed one can have considerable duration of viral failure without meeting CD4 criteria recommended by WHO for switch of ART to second line.

Our response:
We agree with the reviewer and added in the Discussion section (page 9, last paragraph). The recent 2009 revision of the WHO antiretroviral therapy guidelines recommended adherence assessment, repeated HIV VL test, and switch only when HIV VL remains more than 5 000 copies/mL. If HIV VL monitoring is available, switch to second-line cART should be done as soon as possible when treatment failure is established. However, in many countries in Asia, especially those developing countries, frequent HIV VL monitoring and genotypic tests are beyond the limited resource for HIV treatment and care. If CD4 count is the only way for monitoring treatment response, the result of this analysis showed that a patient can have a considerable duration of virological failure without meeting CD4 criteria recommended by WHO for switch of ART to second line. In addition, the effect of delaying switching treatment on longer term outcomes through the possible development of HIV-drug resistance that could compromise the efficacy of later cART regimens remains uncertain

3. Suggest having the authors consider displaying the main table as a figure in stead.

Our response:
We have tried putting Table 3 as a figure (see in the next page). We slightly prefer the table format, but are happy to leave this as an editorial decision.
Figure 2: Estimated CD4 slope (cells/µL/year) by duration of treatment and HIV VL.

Patient 1, 30 years old, no hepatitis coinfection, no AIDS defining illness, and current CD4 200 cells/µL

Patient 2, 30 years old, coinfected with hepatitis, no AIDS defining illness, and current CD4 200 cells/µL
Response to editorial requests

- Please can you include all of the author's email addresses on your title page.

  Our response:
  All the author’s email addresses were added on the title page.

- Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.

  Our response:
  The statement was added after Conclusions section.

- Please can you include the tables in your main manuscript and not just as an additional file.

  Our response:
  The graphs and tables were added in the main manuscript.

- Please include an Authors' contributions section before the Acknowledgements and Reference list.

  Our response:
  The Authors’ contribution section was added before Acknowledgements and Reference list.