Author’s response to reviews

Title: Rapid Development of HIV Elite Control in a Patient with Acute Infection

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Version: 2 Date: 27 Jul 2019

Author’s response to reviews:

We thank the reviewers for their insightful and positive comments on the manuscript. We have addressed all the comments as below which we feel significantly strengthens the paper.

1) The case report indicates that the HIV-1 infected woman did not have any integrated proviral DNA copies in PBMCs. This is an interesting but surprising result. Did the authors used an ultrasensitive proviral DNA assays such as gag ddPCR assays that detect as low as single copy. If authors have not
performed sensitive ddPCR assays, it may be important to check the proviral DNAs as an evidence of reservoir using ddPCR assays.

We agree that the lack of HIV DNA or RNA in cells following establishment of elite control is interesting and surprising.

We used a very sensitive LTR-Gag assay. This is sensitive across all HIV subtypes- the assay has near single copy detection and was performed on millions of cells as reported in the table.

This case is similar to the "extraordinary" controllers (small cohort) as previously published (PMID: 22490332). In this paper some of the patients did not have detectable cellular DNA or RNA. We now discuss this in more detail in the paper.

Our paper is unique, however, in that it follows the development of extraordinary control from initial infection and diagnosis.

2) In Figure 1F, authors have showed that Post ART, CCR5 expression on CD4 T cells was reduced. Authors should comment on expression of CCR5 from the initial stage of viral infection and its further contribution to control of viral infection in discussion part of the manuscript.

This is an interesting point.
The change was minimal however and may reflect natural variation within the assay or timing. CCR5 expression may also fluctuate depending on other factors for example the activation state of the cell.

The expression levels were within the higher range of what has been described in prior cohorts (PMID: 26512140), so less likely to be involved in control of infection.

Reviewer 2: Discretionary revisions

1 The source of infection in the patient is not clear as it was mentioned in manuscript that her partner was not known to be high risk.

The patient had unprotected sexual intercourse one month previously with a male partner in Kenya. She believed that he was high risk and it is presumed that he is the source of infection.

(manuscript amended Case presentation line 86-88 Page 4)

2 The authors mentioned that patient was given ART due to multifocal furunculosis despite continued suppression of virus and stable CD-4 T cell counts. Didn't she receive antibiotic treatment for furunculosis. More clear reasoning is needed why ART was initiated in the patient.

The patient was treated with a number of courses antibiotics and antivirals. There was partial improvement of symptoms with recurrent relapse. The decision was made to start her on ART on clinical grounds. Recent guidelines to initiate ART regardless of CD4 cell count were not in use at the time.

Her skin condition improved significantly with ART administration.
3 Replication competence of the infected virus need to be analyzed.

As detailed in our table and manuscript we were not able to detect any RNA or DNA in cells or any substantial amounts in plasma (0.8 copies not enough to sequence to look for intact virus). The initial viral load was not stored further as was performed for clinical care. We did try to rescue virus from samples when we had prospective collection, but as this is an extraordinary controller, are unable to do so.

4 Serum antibody levels and data on neutralization capacity of those antibodies during the course of infection will enhance the scope of the article.

This is an interesting idea. However neutralization capacity is out of the scope of this study.

Antibody levels are recorded in table 1 using the Vitros test. Two time points are measured before and after ART commencement with antibody binding expressed as a signal/cutoff ratio when we had sufficient plasma sample for such analysis.

5 In Discussion line 156, it was stated that there is an increase in both cellular and humoral HIV specific responses following ART. However, as far as I can see, there is no humoral data following ART. Please explain this.

Increased HIV antibody response following ART initiation was captured using the Vitros HIV test as shown in table 1 (antibody binding expressed as a signal/cutoff ratio).

6 In Discussion line 157, the authors hypothesized increased immune response following ART might be a more generalized immune process that blunted earlier HIV specific responses. Please quote some references if similar observations or related observations were made earlier.

This is primarily our opinion and therefore in order to avoid confusion we have removed this sentence.

7 In Discussion line 168, the authors mentioned "despite delayed increase in HIV specific CD8-T cell responses". However, the manuscript doesn't present any longitudinal CD8-T cell response before ART initiation that could substantiate authors statements. Please explain this.

After careful consideration we concur that more longitudinal data would be beneficial. We have therefore removed amended the manuscript amended discussion and conclusion line 167/168 page 7.

8 More discussion is needed on how immune responses increased following ART initiation despite no
plasma viremia.

Elite controllers are known to produce a strong HIV-specific immune response, more so than in non-controllers (this may in part be responsible for EC) (PMID 20400885). In our paper this is demonstrated in Figure 1.

It is difficult to interpret the change in immune response following ART initiation as this may be contributed by a number of factors reasons including cell viability, assay issues. Although it is an interesting finding we feel that further comment would be speculation. However, the take-home point is that the specific responses were overall high, even prior to ART.