Reviewer's report

Title: Raltegravir decreases inflammatory signaling in brain macrophages in human immunodeficiency virus infection in vitro

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Reviewer: Alan Winston

Reviewer's report:

I reviewed this manuscript with assistance from Dr Jonathan Underwood (jonathan.underwood@imperial.ac.uk) a clinical research fellow in our department.

Little data exists regarding pro-inflammatory and toxicity effects of antiretroviral agents. This study assesses laboratory models of raltegravir to elucidate such mechanisms. This is a well conducted study and should be considered for publication further to the points raised below:

Major comments:

The major limitation of this paper is a lack of comparison with other antiretroviral agents. The authors acknowledge this in the discussion section, however I think this important area really needs highlighted from the start. Many readers will only read the abstract so something should be added here and in the discussion section I wonder if more detailed comparisons could be made with the data regarding other antiretroviral agents. I appreciate cross study comparisons should not be undertaken lightly but given the need to put these results into as much context as possible I do think this should be considered.

In the results section it is curious that TNF alpha is highest in the raltegravir only arm (although p values are not reported in table 1). This isn’t really discussed and is a concern that raltegravir seems to cause a more pro-inflammatory signal than HIV. This needs clarifying/explaining. Looking at the graph this looks like it might be explained by the day 7 results which are way higher than the others and probably skew their fit lines.

Also the lowest cytokines are seen in the raltegravir and HIV group. Lower than controls although no p values. This seems strange and isn’t really explained. Did the HIV and raltegravir kill the microglial cells and that’s why production was lower?

They mention raltegravir doesn’t cause neurotoxicity because the beta-III tubulin wasn’t significantly different which seems fair. However the GFAP is lower in the raltegravir treated group indicating astrocyte damage and again this is not mentioned. Given the crucial function of astrocytes for maintaining the BBB and healthy neurons it seems this may indicate direct toxicity. The pictures also look like there might be toxicity.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests