

September 14, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4739-review.doc).

Title: Microbial translocation, residual viremia and immune-senescence in the pathogenesis of HIV-1 disease.

Authors: *Alessandra Fantauzzi, Francesca Falasca, Gabriella d'Ettorre, Eugenio Nelson Cavallari, Ombretta Turriziani, Vincenzo Vullo, Ivano Mezzaroma*

Name of Journal: *World Journal of Clinical Infectious Diseases*

ESPS Manuscript NO: 4739

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 00759352:

The present manuscript reviews the current knowledge on inflammation and immune activation in the pathogenesis and progression of HIV-1 disease. It focuses on microbial translocation, residual viremia and immune senescence, which should appear in the title. An alternative proposed title could be: "Role of microbial translocation, residual viremia and immune senescence in inflammation and immune activation in HIV-1 disease".

It needs some revision. The paper is well structured but needs a figure and a table to ease its reading, too tough with only words.

There is some confusion in some statements made by the authors. Page 4. Cancers, kidney failure, neurocognitive impairment and a more rapid progression of hep C infection have not been related to long-term antiretroviral treatment (ART). At the contrary, the progression of hep C is actually slowed down by ART. Cancers and neurocognitive impairment are clearly related to HIV-1 and inflammation, not to ART. Finally, some kidney diseases (mainly tubular diseases) are clearly related to ART, but kidney failure is really uncommon. This should be clarified.

Page 9. The standard endpoint PCR uses a detection limit of 20 to 50 copies/mL, not 400 c/mL. Please correct.

Page 8 Clearly MT is not the only cause (if at all) of immune activation. The authors might wish to change "represent the cause of" by "contribute to".

Regarding the studies investigating the intensification with RAL in subjects with suppressed viremia, the authors might wish to cite and comment on Llibre et al (Antiv Ther 2012; 17:355-364). Page 10. When reviewing elite controllers, the authors should cite Chun JID 2013 doi: 10.1093/infdis/jit306, showing that the size of the pool of CD4+ T cells harboring infectious HIV diminished significantly following initiation of ART and rebounded to baseline upon cessation of therapy in elite controllers.

There are some English language typos that should be corrected. The word biased (page 4) should be substituted for “decreased”.

Page 12, the conclusion must be corrected. In its current form its not a conclusion of the article.

Replay

According with the reviewer’s suggestion the title has been changed.

A figure and a table have been added.

On pag. 4 the sentence has been modified and the different contributions on those complications of cART and HIV-1 disease better clarified. As suggested the word “biased” has been changed with the more appropriate term “decreased”.

It is true that the last PCR assays have detection limits ranging from 20 to 50 copies/mL but the more used PCR assay in Western countries (including North America countries) is the standard PCR with 400 copies as detection limit. (Buscher A et al., AIDS Patient Care STDS 2013, doi: 10.1089/apc.2013.0105). However, the sentence on pag. 9 has been changed in a more appropriate manner.

Pag. 8. As suggested, the sentence has been changed with the more correct “contribute to”.

The paper of Llibre et al. has been included in the reference list and commented in the text.

We do not agree with the reviewer’s suggestion to cite the article by Chun et al (JID 2013) in the context of the sentence on elite controllers at pag.10. However, a possible link between this article and the presence of activation markers in elite controllers has been included.

Pag. 12 the conclusions have been changed

Reviewer 00202286:

It is well written and examines the role of immune activation and inflammation in HIV-1 disease. The MS is clearly organized with numerous adequate references. There are only few typos. For example: Abstract: A dot is missing after “immunosenescence” Introduction. Last paragraph: A dot is missing after “process”

Replay

We thank the reviewer for the comments. The manuscript has been carefully reviewed and the typos have been corrected.

Editing suggestions:

The manuscript has been reviewed and a language certificate by professional English language editing company included.

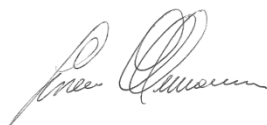
In the References section PubMed citation numbers PMID and DOI are now included.

Please note that all changes made to the original manuscript are highlighted in red in the revised version, whereas all editing changes made by the AIE experts have been accepted and included in the revised version without highlighting.

Thank you again for publishing our manuscript in the *World Journal of Clinical Infectious Diseases*

Sincerely yours,

Ivano MEZZAROMA, MD

A handwritten signature in black ink, appearing to read 'Ivano Mezzaroma', with a stylized, cursive script.

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