

**Name of journal: World Journal of Virology**

**ESPS Manuscript NO: 14852**

**Columns: Meta-Analysis**

November, 28<sup>th</sup> 2014

Xiu-Xia Song,

Science Editor, Editorial Office

World Journal of Virology.

ESPS Manuscript NO: 14852 entitled "Elevated homocysteine levels in HIV-infected patients and its relation with highly active antiretroviral therapy (HAART) usage and B-vitamins status: a meta-analysis."

We are pleased to resubmit the above manuscript which required revision. We thank the reviewers for their critiques which have enabled us to sharpen the manuscript considerably. We believe that we have addressed all the points raised by the reviewers and trust that the manuscript is now suitable for publication in Amino Acids.

Sincerely,

Rafael Deminice, PhD

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Changes are highlighted in red in the text manuscript and are detailed below.

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**To Reviewer 1#**

- 1) The authors thank you the care of the review.

**To Reviewer 2#**

- 1) The papers selected did not present enough information to correlates other parameters with plasma Hcy concentration.
- 2) There is no a typo. "HHcy" means hyperhomocysteinemia. This abbreviation is cited in the text manuscript (introduction, pag 3, line 13).
- 3) *HAART* means highly active antiretroviral therapy. It is also cited in the text manuscript (introduction, first line). There is no HHART in the text manuscript.
- 4) Format errors in the references were checked.

**To Reviewer 3#**

- 1) Units were verified and standardized during the manuscript.
- 2) A final statement reflecting the importance of the study was added in the end of the abstract.
- 3) An explanation about Hcy metabolism and vitamins involvements in its metabolic pathways were added in the introduction (page 3, line 17).
- 4) Studies excluded and the reason of exclusion is described in results. In outcome 1, four of the 16 selected studies were excluded because of the absence of a healthy control group <sup>[40-43]</sup> (page 5, line 26). In outcome 2, nine of the 16 studies selected were excluded from outcome 2 because of the absence of an HIV-infected non-HAART group <sup>[29,30-33,36-39]</sup> (page 6, line 17).
- 5) The papers revised did not present enough information to include vitamin B6 as a subgroup analysis.
- 6) The information that Hcy remethylation to methionine by methionine synthase (MTR) requires folate was added in the discussion (page 7; line 31).
- 7) There are no studies demonstrating HAART modify Hcy metabolism enzymes. It is probably because liver biopsy is an invasive procedure with a relatively high risk of complications. Animal models could enable studies on HAART and Hcy metabolism; however few studies have tested HAART in animal models. A comment in the discussion was included about it (page 8, line 10).
- 8) Transsulfuration pathway explanation was added in the introduction (page 3, line 25).
- 9) MTHFR role in Hcy metabolism was added in the introduction (page 3, line 25). Also, information about MTHFR polymorphism was also included in discussion (page 8, line 29)
- 10) "HHcy" means hyperhomocysteinemia. This abbreviation is cited in the text manuscript (introduction, page 3, line 13).

#### **To Editor**

- 1) Comments were included
- 2) Declaration that a biostatistician work on the data of the manuscript was included in the manuscript on statistics section.
- 3) The title of the manuscript was changed to reach 12 words