# Format for ANSWERING REVIEWERS

April 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

**Title:** Role of host immune responses in sequence variability of HIV-1 Vpu

**Author:** Zafrul Hasan, Doreen Kamori, Takamasa Ueno

**Name of Journal:** *World Journal of Immunology*

**ESPS Manuscript NO: 9988**

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

2 Revision has been made according to the suggestions of the reviewer #01043180

(1) Considering that this becomes relevant at later stages of the review it would be beneficial to include already at the beginning a paragraph on the state of the art of Vpu function and to explain how Vpu has evolved in lentiviral evolution.

*As suggested by the reviewer, we have incorporated the following sentences to the Introduction of the revised version: HIV-1 Vpu is a 16-kDa accessory protein (10) responsible for various functions such as CD4 down-regulation (11-13) and enhancement of virion release by antagonizing tetherin/BST2 (14-17). Interestingly, functionally competent Vpu (with respect to BST-2) were only found in the pandemic group M subtypes, suggesting that Vpu functional adaptation may confer pandemic spread of this HIV-1 subtype (18).*

(2) Would the anti-Vpu antibodies described in 2.1. be expected to neutralize any of the known Vpu functions?

*This is an interesting point of view. We have added the following sentence to discuss this point to the revised version: The epitopic regions for such antibodies reported include 37-50 (30) and 68-81 (28) of Vpu; nonetheless there is no specific Vpu activity mapped to these regions so far. However, considering that Vpu is a small protein (81 amino acids), it is intriguing to test whether such Vpu-specific antibodies can inhibit Vpu functions and subvert viral replication.*

(3) It might be relevant to mention in 3 that it is currently unclear whether any of the in vitro Vpu functions described are really relevant in vivo.

*As suggested by the reviewer, we have added a sentence to describe this point: Finally, although Vpu showed multiple functions in vitro and ex vivo, it is yet clear how and what functions of Vpu are important in viral pathogenesis in vivo.*

(4) The mechanistic paragraph on Vpu and tetherin is not up to date. Please also modify the model presented in Fig.2 accordingly.

We thank for the reviewer to point out this issue. We have corrected the sentences describing the mechanistic pathways of Vpu and tetherin and also modified Fig. 2 accordingly.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Immunology*.

Sincerely yours,

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