Dear Editor, please find enclosed the revised manuscript in Word format (file name "Revised manuscript").

Title: **<u>Validity of the Patient Health Questionnaire (PHQ-2 and PHQ-9) for Screening Depression among HIV patients in Lahore, Pakistan,</u>**

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Name of Journal: World Journal of Virology

Manuscript NO: 76525

Manuscript Type: ORIGINAL ARTICLE

Basic Study

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We emended the paper according to the reviewers' comments. We hope this revision will make our manuscript better to be accepted in your journal.

Each comment has been answered accordingly in the manuscript and each text that has been altered was highlighted red in the revised manuscript. We hope that the revised version will fulfill the requirements for publication in the World Journal of Virology. Thank you very much.

Reply to editorial comments:

Science Editor: The manuscript focuses on the effectiveness of the depression screening patient health questionnaire (PHQ-9) for HIV patients in Lahore, Pakistan, which is very valuable in this field. But there are some problems with the manuscript. 1. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. 2. The format of the table should be a three-line table. 3. The sample of the study is very small, and the depth of the study is not very enough.

<u>Answer:</u> Reference list has been revised and there is no more than 3 references from the same journal. The format of the three-line table has been revised. Depth in the study has been added

Comments:

Reviewer #1:

However there are several crucial methodological issues than impede my support on this paper. Under my opinion, the main limitation I observe in the study is the criteria used as gold standard for diagnosing depression. As authors stated "the PHQ-2 was used as the reference method to diagnose the major depressive disorder". I completely disagree with using this measure (that is included in PHQ-9) as a criteria for calculating ROC curves.

<u>Answer:</u> thanks for the comment. Regarding the methodological issues have been thoroughly reviewed and corrected. A cross-culturally applicable form of PHQ-9 and PHQ-2 is available, but its psychometric properties are still to be validated formally. However, the PHQ-9 and PHQ-2 have not yet been validated in HIV patients in Pakistan. Our primary objective was to measure the psychometric properties of the PHQ-9 and PHQ-2 instruments to diagnose depression among HIV-infected patients. The secondary objective was to estimate the sensitivity and specificity of the PHQ-2 for screening of depression in patients with HIV infection in Lahore, Pakistan.

Furthermore, I could not be able to understand how ROC curves were calculated for PHQ-2 if the gold standard was the instrument itself. Probably the way it is written is confusing, but I regret to say I could not reach this important methodological issue.

<u>Answer:</u> thanks for the comment. The researcher did a face-to-face interview with the PHQ-2 depression screening questionnaire. Following the screening interview, participants completed the PHQ-9 questionnaire with a second study team member who was unaware of the PHQ-2 results. The criterion validity of PHQ-2 was determined using ROC (receiver operating

characteristic) analysis by using the PHQ-9 as the reference standard. Although, we used the PHQ-9 as the gold standard to assess the PHQ-2's sensitivity and specificity as a depression screening instrument. This is our study limitation, and we have mentioned this limitation in the manuscript.

The information on the sample size used in each analysis is also unclear to me. While in the participants section 158 patients are mentioned, later in the method section reference is made to 10% of the sample to complete the analysis with the PHQ-2. If this 10% corresponds to 15-16 patients being used for computing ROC analyses, I consider the sample size to be clearly insufficient.

Answer: Thanks for the correction, the exact number is 158. Information on the sample size used in each analysis is now clearly stated.

Another major issue is related to the hypothesis. I recommend authors to define them, stating which the expected result, supported by previous research is. In addition, considering that the objective of the study is more psychometric in nature (to provide reliability, validity and sensitivity values), it would be desirable that the authors include evidence of the internal structure of the instrument and its relationship with other variables to support this adaptation of the instrument. After considering these important methodological concerns, I cannot consider results or discussion.

Answer: thanks for the comment**.** We have reviewed our hypothesis and redefined our objective of the study, which is more psychometric.

Reviewer 2:

1.Abstract: a. I suggest clearly presenting the terms such as HIV, HIV infection, and AIDS, as defined. HIV patients can be patients with seropositive, who have not necessarily developed AIDS. b. The background and the aim should be expanded to support the methods and the rationale to use PHQ-9 and PHQ-2 in a consecutive manner

<u>**Answer:**</u> thanks for the comment. Theses has been corrected and added in the manuscript.

2. Introduction: I suggest the authors to reorganize the Introduction section, which seems inhomogeneous and dispersive. I think that more information about depressive disorder would provide suitable background here. Thus, I suggest the authors to make an effort to provide a brief overview of the pertinent published literature that offer a perspective on definition, causes and symptoms of depression, because as it stands, this information is not highlighted in the text. Authors should briefly describe the pathogenesis, comorbidity, biomarkers, and diagnosis of depression, antidepressant treatment in general including the mechanism of actions, iatrogenesis, and particular challenge and importance in detecting depression in HIV-positive patients. (https://doi.org/10.3390/bs11080110; https://doi.org/10.3390/biomedicines9070734; https://doi.org/10.3390/biomedicines9010082; doi: 10.1038/s41598-020-73918-z; doi: 10.1016/j.neubiorev.2020.08.010; https://doi.org/10.3390/biomedicines9040340; https://doi.org/10.3390/biomedicines8110509; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7692261/; https://doi.org/10.3390/biomedicines9040403; https://doi.org/10.3390/ijerph19063333). In this regard, I believe that it may be useful to have a general overview of psychiatric mood disorders (i.e., depression, anxiety, and PTSD) and, specifically, of the related symptoms, diagnosis and cutting-edge treatments. For this reason, I would suggest some crucial evidence that will methodologically fit with the present manuscript, as new evidence for the implementation of new methods to treat such disorders (i.e., by the means of Non-invasive brain stimulation techniques (NIBS)) in the treatment in mental disorder in humans: for example, a recent review (https://doi.org/10.1016/j.neubiorev.2021.04.036) described the potential and effectiveness of non-invasive brain simulation (NIBS) to interfere and modulate the abnormal activity of neural circuits (i.e., amygdala-mPFC-hippocampus) involved in the acquisition and consolidation of fear memories, which are altered in many mood psychiatric disorders (i.e., anxiety disorder, specific phobias, post-traumatic stress disorder or depression). Interestingly, another recent manuscript (https://doi.org/10.1016/j.jad.2021.02.076) illustrated the therapeutic potential of NIBS as a valid alternative in the treatment of untypically persistent memories that characterized those patients that do not respond to psychotherapy and/or drug treatments. I may also recommend additional studies that have focused on this issue (https://doi.org/10.3390/biomedicines10010076; https://doi.org/10.3390/biomedicines9050517).

I believe that adding this information will help providing a more coherent and defined background.

Answer: Thanks for the comments. In the introduction section, pertinent published literature that offers a perspective on the definition, causes, and symptoms of depression has been added and mentioned in the introduction text. In the introduction section, we have briefly described the pathogenesis, comorbidity, biomarkers, and diagnosis of depression, antidepressant treatment in general, including the importance of detecting depression in HIV-positive patients. The introduction text has also mentioned a general overview of psychiatric mood disorders (i.e., depression, anxiety, and PTSD) among HIV patients. Relevant literature related to new methods to treat such disorders (i.e., using Non-invasive brain stimulation techniques (NIBS)) in treating mental disorders in humans has also been mentioned in the introduction text.

3. Study design: I suggest fully expanding the study design including the sequence of tests and the number of patients.

Answer: Thanks for the comments. Theses has been corrected and added in the manuscript.

4**. Results: In my opinion, this section is well organized, but it illustrates findings in an excessively broad way, without really providing full statistical details, to ensure in-depth understanding and reliability of the findings**

Answer: Thanks for the comments. Theses has been corrected and added in the manuscript.

5. I think the Conclusions paragraph, despite being well organized, is too thin and does not clearly describe what the authors think is the take home message. I believe that this section would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it is very descriptive but not enough theoretical as a discussion should be. Authors should make an effort, trying to explain the theoretical implication as well as the translational application of their research.

Answer: Thanks for the comments. The Conclusions paragraph has been revised and added more literature.

6. Figures and Tables: please provide an explanatory title and caption for each figure and table within the text. Overall, the manuscript contains two figures, four tables and 45 references. In my opinion, the number of references it is too low for an original research article, and this issue may prevent the possibility of publishing it in this form. However, the manuscript carries important value presenting the validity of PHQ-9 to detect depression among patients with HIV infection.

Answer: Thanks for the comments. The Conclusions paragraph has been revised and added more literature. Explanatory title and caption for each figure and table within the text have been added. The number of references has been increased for an original research article.

Thank you for consideration the review.

 Sincerely yours,

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