Peer-review Comments and Author Responses

Manuscript “Pursuing Dementia in People Living with HIV/AIDS: Prevalence and Associated Factors”

Reviewer 1:

1. Cross-sectional design: The cross-sectional design used in this study does not allow for causal relationships to be established between variables. It only provides information on the prevalence of HIV-associated dementia and the associations between variables at a single point in time.
Non-probabilistic sampling: The use of non-probabilistic sampling in this study truncates the generalizability of the findings to the population. The sample was selected based on specific inclusion and exclusion criteria, which may not represent the overall population of people currently diagnosed with HIV.
IHDS cutoff: The study used an IHDS cutoff of 10 as a risk factor for only dementia because this cutoff does not apply to mild and moderate neurocognitive impairment. However, it is unclear why this cutoff was chosen; authors could elaborate more on this decision.

We know that the sample size and the non-multicenter design do not allow for generalizability and casual relationships; this is addressed in the limitation section of the article.
We clarified the cutoff in the article.]

Reviewer 2:

2. Regarding the nomenclature "combined antiretrovirals (cARV)," I would change it to the most commonly used HAART – Highly Active Antiretroviral Therapy.

We adjusted cARV to HAART;

3. In the abstract methods section, you mention: We evaluated 134 patients living with HIV/AIDS. AIDS was not part of the exclusion criteria?

We removed AIDS as it is part of the exclusion criteria;

4. References need to be organized according to the journal format. In the introduction, you start with numbers 2, 4, and 7, but we do not have the numbers in the reference list. Please, correct them.

References were adjusted

5. Regarding: "The exact central nervous system viral infection mechanism is unknown, but researchers believe in multiple pathways". Could you give some examples with references here?

A paragraph was added explaining the pathophysiology with references.

6. With regard to: "The UNIFESP Ethics Committee approved this study, and all patients received a consent form before enrollment". Could you describe better how recruitment was done? Which sampling method you used? Could you also put the number of the Ethics Committee approval?

Issue addressed in the text.

7. Minor changes in "hepatitis C coinfection, hepatitis B coinfection" and ”alcohol dependence, drug dependence". "any past or current medical history of CNS" This is the first time you mention the abbreviation CNS; you need to specify you are referring to the central nervous system. Please, check all other abbreviations as well
"any previous or current mental health"

Change to (hepatitis B or C coinfection);
Change to alcohol or other drugs dependence;
"any previous or current mental health" disorder?
All suggestions were addressed.

8. Could you elaborate more on why you chose the significance of 0.20 instead of 0.05? And why use Poisson multiple regression test?

Our biostatistician suggested these after analyzing our study design.

9. I see a problem with the definition of “HIV risk behavior” putting sexual orientation inside. I would suggest changing it to only sexual orientation and putting an asterisk for the case of blood transfusion as the only case you had of HIV transmission besides the sexual route. We need to bear in mind that homosexuality was considered a risk factor for HIV, and that led to the stigma within the LGBTQ+ community. However, we cannot say it anymore. That’s the problem I see when you categorize it as “HIV risk behavior”. Another possibility is to categorize all the variables for HIV transmission (sex or blood transfusion) and then have separated one for sexual orientation (hetero, homo, or bi). I like this last suggestion the most.

Suggestion addressed.

10. One question: did you consider in your analyses the patients who have failed treatment due to non-adherence? That can influence the risk of dementia since they would have had blips in their viral load.

We did not consider them once we wanted to evaluate the risk of developing dementia in a patient without obvious risks as non- HAART treatment and HAART failure.

11. In the discussion, you could also mention that CNS can be a viral reservoir for HIV due to low penetration of HAARTs because of the blood-brain barrier.

Information added.

12. In the limitation, add that you did not analyze or take into account failures of treatment and the time frame they had blips in their viral load among participants.

Information added.

Reviewer 3:

13. Introduction:
- The introduction is clear and very well-written. More than any major changes, the manuscript would benefit from an extra paragraph explaining more about the natural course of the HIV infection and its subsequent neurological affection.

Paragraph added.

14. Methods:
- The methods are not clear in stating if subjects were chosen from a database and interviewed again; or if they extracted the information from electronic health records with interviews done before. A clear statement specifying the data collection would be beneficial for the clarity of the manuscript.

Method clarified.

15. The cross-sectional study using the electronic health records from 2011 to 2013 is over 10 years ago. Although it could be interesting to see these specific years, it would be better to have a more recent data to compare if available. However, the authors could also explain to the reader why they selected these years to perform the study. And address any possible limitations and bias this could bring to the study.

This study was done ten years ago, so the health records are from this time frame. Before submitting the article, I reviewed the most recent info, and there was nothing new that could change the study.

16. A more detailed description of the population served by the hospital is advised. As a single center, outpatient sampling could be highly biased, it is important for the reader to know the specific population where the study population came from.

Yes, this description is characterized by the exclusion and inclusion criteria.

17. Were the interviews performed by the same clinician? Or how did the authors address the possible variability between the different raters? If this is a variable, it would be important to analyze and consider them in the subsequent results section. If the authors do not believe the questionnaire for diagnosing and evaluating any disease of the HAND spectrum could be biased or have high interrater variability, it would be important to state this in the text, as well as the reasons and literature supporting this.

All interviews and analyses were done by the same clinician. I added this information to the text.

18. Results and Tables
- The operational definition of dementia used for table 1 should be explicitly stated in the text and the table.

Information added.

19. A brief summary of how to interpret the CPE and other mentioned neurocognitive evaluations is advised; as some readers would not be as familiar with this diagnostic and evaluation tools.

Information added.

20. It is not stated why almost 90% of the patients that could be included (1437) were excluded from the analysis. A small flowchart specifying these reasons would be recommended.

They were excluded according to the inclusion and exclusion criteria.

21. An association of dementia and level of education has been repeatedly found by population and ecological studies in healthy people. However, as the authors do have a middle-age adult sample size, it would be interesting to see how the rates of dementia compare to age-matched adults in the literature.

Thank you.

22. In a similar manner, as the authors have available the different education categories for the population, it would be interesting to run a logistic regression analysis with these parameters in addition to the binomial analysis that the authors performed.

Thank you.

23. Discussion
Although the results are very interesting, is important to emphasize that prevalence is the strongest parameter. The other posthoc analysis do expose many interesting questions, but it is important to emphasize that the results might be false positives from doing repetitive analysis. And although I do find adequate due to the nature of exploratory study to not adjust for multiple testing, it is important to emphasize this major limitation through the discussion.

I added this information.

24. In a similar manner, although there is biological plausibility of the risk factors found by the authors, it would be advisable to compare how the results of the risk factors compare to similar articles published in the literature. In these days, biological plausibility it is common across many different risk factors that during experimental and observational studies do not confirm. Therefore, it would be important to extend the literature review to discuss this in the manuscript.

Thank you!

25. The discussion has a very strong background in terms of the literature review in Brazil. However, based on the introduction, the discussion should also compare published literature elsewhere in this topic.

Information added.

26. Minor comments:
In the first paragraph results section, I don't consider it not necessary to specify the median in the text. You could calculate the IQR and specify that most of the patients included had a normal BMI.

Thank you.

27. Please delete the "please add" part in the funding section.

Part deleted.

28. If all the authors have the same affiliation, then they all can use the same superscript "1", instead of adding a superscript per each author.

Issue fixed.

29. Small improvements in punctuation can be performed in different sections of the text.

Thank you.

Reviewer 4:

30. Table 1 has words in Portuguese.

Words fixed.

31. Why didn't you compare the type of ART that the patients use? Should be interesting if they're using the first, second, or third line.

We did not have a sample large enough to do this type of comparison, according to the biostatistician.

32. What serotypes of HIV were recognized in the patients?

Only serotype 1, which is now clarified in the text.

33. Did you adapt the IHDS to your patients?

The IHDS does not have to be adapted, so it can be used worldwide.

34. Where do you analyze the variables?

I analyzed with the biostatistician.

35. Where do you collect the information?

All literature information was collected from PubMed and Cochrane. Patient information was obtained from patient records from the Universidade Federal de Sao Paulo (UNIFESP) Infectious Disease Outpatient Clinic.