Author's response to reviews

Title: What determines health-related quality of life among people living with HIV? An updated review of the literature and practical recommendations.

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Author's response to reviews: see over
Response to the reviewers

Title
What determines health-related quality of life among people living with HIV?
An updated review of the literature and practical recommendations.

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Dear Editor / Dear Referee

Thank you for critically reviewing our manuscript and providing valuable and supportive suggestions in order to improve this research article. We have addressed each of the reviewers’ comments in turn to the above-mentioned manuscript, and numbered our responses item per item according to the reviewers’ questions. If applicable, all changes made throughout the manuscript are described and shown using ‘italic’ notation.

Yours faithfully,

Sophie Degroote
Editor’s comment

1. A review manuscript may benefit from the guidelines for a systematic review (see PRISMA guidelines). Especially the flow chart may be useful. If not considered, the authors should argue this in the letter to the Editor.

   We certainly agree. However, we have chosen to make a narrative review. In our opinion this already would be of particular value for the target audience. Although not applying the methodology of a systematic literature search, we believe this narrative provides sufficient relevant information dealing on the topic discussed.

2. The titles of the tables and figures should be meaningful so that the table/figure can be read without the text. Additional information can be given in the legend under the table/figure.

   This is correct. We checked and adapted the titles and we removed parts of titles to the legends making them more comprehensible and understandable.
Reviewer's reports

Reviewer: Ward Schrooten

Reviewer's report:

Major Compulsory Revisions:

1. In the results sections several (if not most) variables had contradictory effects when comparing different studies. “Concluding from this review, socio-economic status, immunological status, presence of symptoms, (psychiatric) comorbidity, social support and adherence to HAART showed to be the main determinants of HRQoL in PLWH. “ as a discussion is too straightforward and lacks nuance.

   We agree with the reviewer. We can not conclude that those variables are the main determinants of HRQoL; results in the review rather indicate that there is consensus about the fact that they do influence HRQoL.

   We have adapted this sentence:

   Many determinants have been found, and it is not clear which determinants are the strongest predictors for HRQoL. Nonetheless, there seems to be a consensus about the effect of socio-economic status, immunological status, presence of symptoms, (psychiatric) comorbidity, social support and adherence to HAART.

2. It is remarkable that fear/anxiety did not come up as a separate variable in the results section, as anxiety among HIV infected individuals could be an important factor determining quality of life. At least this should be explained in the discussion section.

   Thank you for raising this issue. The reason that we did not include fear/anxiety as a separate variable, is that only one study included in this review really addresses the question whether fear/anxiety negatively impacts HRQoL.

   Osowiecki et al. (2000) as well as Rodriguez-Penney et al. (2013) report on the negative impact of high POMS (Profile of Mood States) scores. Those scores include anxiety, along with five other mood states.

   Three of the included articles (i.e. Cederfjall et al, 2001; Zinkernagel et al, 2001; Preau et al, 2007), assessed anxiety separately. However, Cederfjall et al. and Zinkernagel et al. used anxiety as a dependent variable, and did not investigate the effect of anxiety on HRQoL. Only Preau et al. have identified anxiety as determinant of poor mental and physical HRQoL. We have added this to the results (‘Depression and anxiety’):

   The prevalence of anxiety disorders in PLHIV is higher than in the general population and it is associated with depressive symptoms [14, 56]. Anxiety was found to be associated with a diminished physical and mental health [18].

3. The limitations of the instruments used should be discussed. Are any new variables currently being studied which could complement these instruments? For example, the concept of resilience could be discussed (e.g. Motivation, Management, and Mastery: A Theory of Resilience in the Context of HIV Infection Joseph P. De Santis, Aubrey Florom-Smith, Amber Vermeesch, Susana
Thank you for this remark. We have added an extra section in the discussion about the HRQoL instruments, including their limitations (e.g. not taking into account resilience). For some ‘older’ variables, such as coping and stigma, it is already known that they are important for PLHIV. Likewise, however, they are mostly not included in HRQoL assessments.

4. In the discussion section it would be interesting to put the findings in a wider context, comparing with studies done in other diseases such as cancer.

We thank the reviewer for this valuable comment. We have included findings from review studies in other diseases:

These partly correspond to determinants of HRQoL of people living with other diseases. In patients with Crohn’s disease, epilepsy, Parkinson’s disease and aneurysmal subarachnoid haemorrhage, advanced disease stage (cfr. immunological status) was found to be predictive for impaired HRQoL [77-80]. Disability (cfr. presence of symptoms) was a determinant of HRQoL in patients with Crohn’s disease, Parkinson’s disease and aneurysmal subarachnoid haemorrhage [77-79]. Depression was negatively associated with HRQoL in patients with epilepsy, Parkinson’s disease and aneurysmal subarachnoid haemorrhage [78-80]. Presence of comorbidities was associated with lower HRQoL in patients with epilepsy and in long-term survivors of colorectal cancer [80-82].

5. An attempt is made to translate the findings into recommendations. It is not clear how these recommendations follow from the findings in this study (it rather feels these recommendations were forced into the discussion section). In any way the practical recommendations are described too briefly to provide any insight, or even to be announced in the title of the paper.

We understand the reviewer’s comment that the recommendations were not sufficiently elaborated, and could as such be potentially mis- or even overinterpreted. Therefore we have chosen to change these recommendations towards a more critical reflection about the HRQoL instruments currently used in HIV (cfr. Remark 3)

Minor Essential Revisions:
Typing errors:
1. Page 5, last paragraph: “…did not found an (independent) …”
   Ok, thank you.
2. Page 6, first paragraph: “However, physical health improves more in patients in whom HAART was started at CD4 <200 cells/μl than in patients with CD4 <200 cells/μl or >350 cells/μl, “ : this sentence is not clear (twice <200 cells)
   Ok, thank you.
3. Page 7, first paragraph: “... trough which treatment…”
   Ok, thank you.

Discretionary Revisions:
1. Developed countries: what is the definition of “developed” countries? Since
this is mostly based on economic criteria, it is better to use terms like “economically more developed countries” or “high income countries” depending on how the included countries were selected.

We agree, the term ‘high income countries’ is more correct. We have changed the formulation.

2. Though obvious from the introduction, the methods section should include “investigate HRQoL in HIV infected individuals” as one of the criteria for selection of articles (as HRQoL in other diseases is not included)

Ok, thank you. This criterion was included.
Reviewer: Christiana Noestlinger

Reviewer's report:

Review QoL HIV
1. Is the question posed by the authors new and well defined?
The objective of this paper is clear, and scientifically very relevant, both from a public health and from a clinical perspective. The latter, because patient reported outcomes have gained increasing importance as an additional criterion in the choice of therapeutic strategies for the management of HIV infection in high-income countries. As there is no consensus yet, as the authors rightly point out, this paper is important for guiding clinicians in making such choices by providing a methodologically sound overview of the currently available instruments to measure HRQOL, and by drawing relevant policy conclusions. The authors also mention this objective, i.e. providing practical suggestions for interventions that will improve HRQOL.

In my review I will point out the reasons, why I doubt that the authors have reached this second objective, and I will make suggestions of a more modest and realistic achievement that this paper could reach.

The question or main objective of the paper may not be totally new, but evidence-based guidance on the use of HRQOL instruments in the HIV field is missing.

We are grateful to the reviewer for providing this positive and constructive reflections.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
With respect to the method section, the following remarks that could substantially improve the paper.

1) It should be clearly stated that it concerns a non-systematic review and the reasons should be given why this has been the method of choice.

   Thank you for this comment. We added extra information in the methods section.

   A narrative review was performed. Results of the searches were not systematically registered. The global search strategy was to search the databases PubMed, Web of Science and The Cochrane Library...

2) Point 5 of the used selection criteria refers to: “...using a validated HRQOL instrument”; the abstract also lists these instruments between brackets. I think that the list of validated scales should be included under results, and not under methods, unless the authors have a specific reason to exclude validated instruments; in this case, they should also provide the rationale for it.

   We agree, this could indeed be interpreted as if we excluded certain instruments, while this was not the case. We removed that part from methods to results.

   For instance, the validated instrument PROQOL-HIV (Duracinsky et al. 2012; see link to JAIDS below) has not been included. Normally, the literature search should have delivered both the instrument as such, and studies which used it (e.g. Herrmann et al. 2013; an Australian study)

   Thank you for this additional information. We have found one study in which the PROQOL-HIV is used; we included that study in the results.
3) Point 6 of the inclusion criteria does deserve further explanation: why would studies/papers be excluded that use other statistical methods than multivariable regression analysis to identify determinants of HRQoL?

We did not include qualitative research because the methods used and the variables studied would be difficult to compare with the studies using quantitative analyses. We added this information to the inclusion criteria, and briefly included this issue in the limitations section of the paper.

Concerning quantitative research, we have found an amount of papers in which only bivariate analyses were performed to identify variables associated with HRQoL, which, to our opinion, is not a sound method and can result in oversimplified conclusions. Multivariable regression is more powerful to detect determinants independently associated with HRQoL, as different variables are combined.

4) The authors say that they used a priori framework with four categories of determinants (p. 3). It would help the reader if those categories were mentioned directly under the method section. In addition, while those categories intuitively make sense, it should also be stated how the authors derived at them.

Ok, thank you. We specify the categories also in the method section, and added information about how we derived at them.

A priori, a framework with four categories of determinants was made: socio-demographic, clinical, psychological and behavioural determinants. Those categories were chosen by analogy with the research on HRQoL performed in our hospital department, which examines those four categories of variables [6].

3. Are the data sound and well controlled?

The results are largely descriptive, in that the authors do not make attempts to compare the studies included in this review in terms of the studies’ methodology and soundness. While this is a non-systematic review (see above), the authors could try to document more systematically the different studies included, rather than just listing the results, and they should critically assess the methodologies applied in the different studies included.

For instance, studies could be compared in terms of the methods they used (i.e. studies with a longitudinal design, studies with control groups, representativeness of the sample, HIV-specific or a general HRQOL instrument, etc.). This way, the findings could be weighed in terms of their methodological soundness and robustness; as of now, the reader unfortunately is left with mixed (and “confused”) feelings, what to make of the results: one study reports a specific finding, another study reports the contrary finding, and the authors do not provide enough information on those studies to judge the results. In the end, one remains with the impression that it all is quite complex and partially contradicting.

This is not surprising, but such a review should undertake the endeavor to analyze more indepth: in which setting, which target population (i.e. sub-group of HIV patients) was a specific study undertaken, or measured with an HIV-specific or a general HRQOL instrument? To improve on this aspect, I would recommend to include a table that specifies per study the following items: study (authors); place, sample-size (incl. gender specifications/age), formal measures (validated HRQL scale); study design (e.g. crosssectional, longitudinal, case-control...); main findings.

This will be a long table, but it would add to the transparency of this review and provide relevant guiding for the reader to better understand the conclusions that are drawn in this
paper. Such a table would also be helpful to make the text more consistent: now the authors
sometimes give the sample size in the text, sometimes they don’t. Sometimes they refer to
the study population, sometimes they don’t. While this choice now seems to be arbitrary, all
this information could be provided in the table, which would improve at the same time the
flow of the text.

We agree with the reviewer, such a table significantly improves the manuscript. Therefore,
we have included a table in which the above mentioned features of the included studies are
reported. We hope this can be a practical guide and provide a clear overview for the reader,
on the one hand providing more details and on the other hand clearly comparing the studies’
methodology. We have also removed unnecessary study details in the manuscript text.

In terms of the description of the results of the included studies, the authors should more
clearly refer to whether it concerns a previous finding or an interpretation. Quite often
expressions are used, such as for instance on p. 4 “...it may also affect the self-esteem and
social contacts of PLHIV”. It is not clear if that is an interpretation or a study results, in this
case relating to the study cited under (45).

Thank you. We had chosen those formulations to express the uncertainties inherent to
scientific research, but some formulations can indeed be too hesitating. We screened for
such expressions and changed them where possible.

Other examples for this are for instance

- on p. 7: “…symptom status would be…” (second para)
  Ok, thank you.

- on p. 8: “…coping may be ineffective” (first para)
  Ok, thank you.

The authors should check carefully how they use the term “negative predictor”, and should
always indicate the direction of an association, to which they refer to. For instance, p. 4:
“older age was a negative predictor for mental health...”: does this mean that older age
predicted impaired mental health? Or does it rather mean that there is a negative
association between old age and “good” mental health? Such formulations need to be very
precise.

We use the term ‘predictor’ only for longitudinal data. ‘Older age is a negative predictor for
mental health’ means that older age negatively influences mental health over time. We have
clarified this by changing the formulation.

“while older age was associated with a decrease in mental health after six months in another
study”

See also p. 5: negative predictor for physical health? Should be defined.

We have clarified this by changing the formulation.

However, a stable partner was also found to be positively associated with mental health after
one year
See also p. 7: mental health change after 6 months à which direction?

We have clarified this by changing the formulation.

An education of less than five years is negatively associated with mental health after six months.

Results on psychological factors:
- p. 7: sentence last para: “…some authors only find an association with mental health”. Clarify statement, since depression is a mental health condition.

One could expect that depression also affects physical health (e.g. sleep problems, less appetite leading to a poor physical condition).

Some authors only find an association with mental health, and not with physical health [9, 15, 16, 54] although depression can also cause physical problems (e.g. less appetite, sleep disorders...).

- p. 8: refer to coping styles, and not coping as such, because it is the way HOW people cope that determines the extent to which they are able to integrate HIV into their lives.

Ok, thank you. We have changed the term.

- Check the following sentence: “...an internal HLOC is a predictor of a better physical health and a powerful others HLOC predicts...” ??? Something must be missing here.

Thank you. Something must have gone wrong here. In our version of the manuscript, the sentence is:

“An internal HLOC is a predictor of a better physical health and a powerful others HLOC predicts a lower mental health [25]”

- Social support (p. 8): mediated by instead through the intermediate variable Depression

Ok, thank you.

- Other (health care, disclosure, stigma): “PLHIV should be encouraged...” à to do what? “AND “before they are confronted” à they may not always have the choice, since stigma and discrimination are external condition (except for internalized stigma).

We have changed this part. Indeed, these are external conditions but people can be reinforced to better cope with this.
PLWH should be prepared and reinforced by health care professionals before their disclosure and before they are confronted with stigma and discrimination in order to better cope with these difficulties [45].

- P. 9, disclosure: there is also quite some evidence that disclosure can have an overall beneficial impact, so the statement ‘disclosing seropositive status was found to have negative effects on both physical and mental health” should be put into perspective. Although this should be discussed under the discussion section; see below comment son discussion section.

Thank you for raising this issue. We agree, and expanded this part.

Disclosing seropositive status was found to have negative effects on both physical and mental health [18]. The latter relationship remains, however, unclear, because disclosure can also be beneficial for the patient’s mental and physical health (mainly through social support) [64]. However it can potentially be related to the fact that people with worse HRQoL have to disclose their seropositive status because of the symptoms, and may feel forced to do so instead of voluntarily doing so.

Results on adherence:

- p.9; adherence: consider revising last sentence: “PLWH with better adherence . . . have a better virological and immunological control and therefore report a better HRQOL”, but in my understanding this refers rather to outcome than to control?

Yes, that is true. We had chosen ‘control’ because it refers more to the fact that the patient (at least for some part) can control his/her virological and immunological response by his/her adherence. Even so, we changed the sentence.

- Last sentence, try to reformulate; quite sloppy...

Ok.

These difficulties originate in a low self-efficacy, a high pill burden, difficulties to incorporate the medication moments in daily activities, experiencing side-effects...

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   à see also above; the comprehensive table would add to transparency.

Ok, thank you.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   There are two main points with respect to the discussion, which I believe could substantially improve the manuscript:
   Firstly, the discussion should be a critical reflection of the main findings, in terms of methodology and quality of the studies included; for instance, it is striking that HIV-related stigma and discrimination gets comparatively little space in this studies while we know from a body of evidence emerging from other research on the psychosocial situation of PLHIV, that it does have a major impact on PLHIV’s lives. Apparently currently used HRQOL measures have limitations in this regard; I would find it interesting to learn whether HIVspecific
HRQOL instruments are more adapted than the general ones to detect the HIV-specific burdens, and whether general instruments, if used, should be complemented with specific questions on things such as stigma, disclosure (see remark above, referring to p. 9), or HIV-specific symptoms for instance.

Indeed. We thank the reviewer for this suggestion. We reworked both the introduction and discussion by adding some parts putting the issues mentioned (particularly regarding the instruments and their limitations) in better context.

Secondly, the link between recommendations given referring to specific interventions and the results is not well established. While there is a certain connection between the identified factors and intervention content, it can be questioned whether such interventions would effectively increase the HRQOL. Instead, one would have to scrutinize the available evidence and assess to which extent whether they have achieved an increase in HRQOL.

In addition, the interventions described include the whole array of interventions possible, without any critical reflection on their theoretical base, whether they have been developed using a sound methodological approach, whether they have been tested, and for which behavior-specific or general HRQOL-outcomes (most interventions typically focus on one or multiple specific behavioral outcomes rather than improving HRQOL in general, though one could argue that this is a deficit).

It is clear that it is not (and cannot be!) the scope of this paper to present that type of evidence, however, the way the interventions now are listed is too simplistic. In addition, one remains with questions such as how do we know that these interventions will lead to the desired outcomes/improvements in HRQOL and how to prioritize between the different types of interventions, since there are so many targeting different levels?

For the scope of the paper’s discussion and conclusion section, I recommend to be less ambitious and base the discussion on the findings of this review. This would lead to guiding the reader on issues such as which HRQOL instrument to use in which target group and setting, especially in real life studies, or when added to clinical studies as a useful additional patient-reported outcome measure. This would already represent a very useful achievement for both public health researchers and clinicians. Because in the absence of a ‘gold-standard’ in HRQOL, that type of guidance really would be needed.

We agree with the reviewer and changed the discussion accordingly. We omitted the part about possible interventions, and included a critical reflection about the HRQoL instruments used in the studies.

More detailed comments pertaining to the discussion section:
- The discussion should start by stating explicitly the main findings (second paragraph, last sentence), even before mentioning the study limitations;

  We agree, thank you. We have changed the sequence of the discussion.

- The figure should be mentioned in the text and should be explained.

  Ok, but we removed the figure, as this was not relevant anymore.

6. Do the title and abstract accurately convey what has been found?
The abstract should be rewritten after having adjusted the main text. The validated scales should be included under the result section.
Ok, we have changed the abstract appropriately.

7. Is the writing acceptable?
The manuscript should be carefully combed through once more and language-edited. For instance, the use of the tenses is not consistent throughout the paper. Results are described both in the present tense and in the past tense, but the latter is preferable when describing what the study found out. There are also quite some “neerlandisms’ in the manuscript, see for instance p. 6 “stadium”; p. 3 “authors argument...”, or p. 11 “consequently”...

Ok, thank you.

Detailed comments:
p. 4, 2nd para: explanations instead of motivations
   Ok, thank you.
p. 5, 3rd para: It can provide structure
   Ok, thank you.
p. 5, last line: find instead of found
   Ok, thank you. We kept the past tense, ‘have found’.
p. 6, first para: patients who started HAART
   Ok, thank you.
p. 6, first para: in a recent study instead of a last study
   Ok. We meant ‘the last one concerning CD4 cell count’, but changed it into ‘in another study’
p. 6, first para, last sentence: clumsy, reconsider formulation
   Ok, thank you.
   Over time, PLWH develop other perceptions and expectations about HRQoL and may consider their health status as acceptable [39].
p. 6, second para: MHS abbreviation not explained
   Ok, thank you.
p. 6, heading and 3rd para: stadium? à HIV disease progression, staging.
   Ok, thank you.
p. 6, ART treatment: consistent use HAART and ART throughout the paper?
   Ok, thank you.
p. 6, ART treatment: use of “meanwhile”?
   Ok, thank you.
p. 6, last para: recent studies mainly show a ...
   Ok, thank you.
p. 7: GB, abbreviation not explained
   This is a rather difficult explanation of an abbreviation and was therefore not included. GB Virus C is named after a surgeon, G. Barker, who fell ill in 1966 with a non-A non-B hepatitis which at the time was thought to have been caused by a new, infectious hepatic virus.

p. 8, first para: effective in reducing
   Ok, thank you.
p. 8, last para; Full stop after (59)
   Ok, thank you.
p. 9: “has been relatively more studied” than what?
   Ok, this was clarified:
   Quality of life in HIV positive drug users has been relatively more studied than in tobacco and alcohol users, because IDU is a risk factor for HIV transmission.

p. 9: “never users” à term?
Ok, we changed ‘never users’ to: “persons who never used drugs”

p. 9, first para: direct or indirect impact, not directly
   Ok, thank you.

p. 9, last para: associations are OR: were found to be inconclusive (if all is written in past tense)
   Ok, thank you.

p. 11: check first para, line 3... something omitted here?
   Yes, thank you.
   *The literature search is not integrally documented, and as such impossible to reproduce.*

p. 11, second para: varied from one single question to ...
   Ok, thank you.
Reviewer: Jessika Deblonde

Reviewers report:
Thank you for giving me the opportunity to review this interesting and timely paper with the well-defined objective of providing an overview of determinants influencing HRQoL.

Major compulsory revisions:
1. The introduction should make reference to the variety of existing HRQoL instruments.

   We agree, as this was another reason to conduct this review. Moreover, we have now added an extra part in our discussion concerning HRQoL instruments used in PLHIV.

   Although different studies identified factors associated with HRQoL, there is no consensus about the main determinants. In addition, a variety of HRQoL instruments are currently being used in PLHIV. In this review, we examined determinants reported to be associated with HRQoL in PLWH and we critically discuss the use of HRQoL instruments.

2. There is a discrepancy between what you describe in the methods and the first paragraph of the discussion. The methodology refers to all the steps of a systematic literature review (databases, keywords, inclusion and exclusion criteria) whereas the discussion refers to this study as being a non-systematic review. Can you explain which (type of) papers you did not document in this review? In order to allow a contextualization of the findings of your review, you should then describe – at the start of the results section – the article selection process, along with some other features of the selected papers (number of papers, type of study, country, ...).

   The reviewer is correct and we apologize for this confusion. We have performed a narrative review. The searches were done at different moments and the number of retrieved articles were not systematically recorded. As such, we do not meet the criteria for systematic reviews.
   We have now included an extensive table providing methodological features of the included articles and in the inclusion criteria, we mention that we only included quantitative studies.

3. In contrast to the results section, which is very detailed, the discussion is (too) concise and rather poorly elaborated. Taking into consideration the title of your manuscript which refers to ‘practical recommendations’, I would expect a more detailed elaboration of the proposed categories of interventions/recommendations, including the link with figure 1.

   We agree with this remark. In order to combine the comments and suggestions from the different reviewers, we have chosen to largely omit the practical
recommendations (and Figure 1) and to elaborate in more detail on particular issues. For instance, we included an additional section about the use of HRQoL instruments.

4. There is a need to better explain how to translate the findings from this review into recommendations because the way is not straightforward. For example:

- p.6: “Physical health improves more in patients in whom HAART was started at lower CD4 count because the physical health at baseline is worse.”

Notwithstanding, clinical studies have indicated that maximum benefit in terms of reduced morbidity and mortality is obtained when HIV infection is diagnosed and treated early. Based on this, the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2013) promote expanded eligibility for ART with a CD4 threshold for treatment initiation of 500 cells/mm3 or less.

Ok, this issue deserves indeed more explanation. We have changed the text:

However, physical health improves more in patients who started ART at CD4 <200 cells/µl than in patients with CD4 200-350 cells/µl or >350 cells/µl, because their physical health at baseline is worse [38]. Current guidelines recommend nonetheless to start ART early (i.e. 350-500 cells/µl), because there is evidence that this results in reduced progression to AIDS and reduced mortality.

- P.6: “A lower mental health over time can arise in cases where longitudinal follow up resulted in successful control of HIV.” So, this means that … ?

This needs indeed to be ‘translated’. We have added the following:

For health care providers, it is important to monitor mental health continuously, irrespective of the physical condition of the patient.

- p.7: “PLWHA with a GB virus C infection reported even a better quality of life than PLWHA without GB virus C infection.” So, this means that … ?

Thank you, this is another issue that deserves more explanation.

Authors reason that patients’ HRQoL can be more affected by socio-economic and psychological factors than physical illnesses as HIV or hepatitis C, as the latter have become manageable diseases [17], or they may be a more favourable course of HIV infection in patients with GB virus C infection [52].

- p.9: “No alcohol use was a predictor for a lower physical health.” So, this means that … ?

This sentence should indeed be nuanced, otherwise wrong conclusions could be drawn.
A causal relationship between light to moderate alcohol use and a better physical HRQoL is, however, not very plausible. Light to moderate alcohol use could rather be seen as an expression of risk behaviour, for which a certain degree of functional status is required [15].

- p.9: “Disclosure was found to have negative effects on physical and mental health”. So, this means that … ?

Thank you for this example, we reformulated that part of the text:

However it can be caused by the fact that people with worse HRQoL have to disclose their seropositive status because of the symptoms, and may feel forced to do so instead of voluntarily doing so. PLWH should be prepared and reinforced by health care professionals before their disclosure and before they are confronted with stigma and discrimination in order to be able to better cope with these difficulties [46].

Minor essential revisions:
1. In the title, you mention ‘practical recommendations’ whilst in the discussion you give examples of ‘interventions’. These words have a different meaning and you should consequently use the right word.

   We agree, but as we now changed that part, we also changed the title and so this won’t be a problem anymore.

2. P.5, §3, line 3-5: this sentence is not very clear. You probably mean that lower education represents poorer ability to understand therapy recommendation.

   That is right, thank you. We have changed the sentence:
   
   It is possible that a lower education is a proxy of a lower socio-economic status in general, but it could also represent a poorer ability to understand the therapy recommendations [20].

3. p. 6, line 4: typo, I assume that you mean CD4 >200 cells (instead of CD4<200 cells)

   Yes, thank you. We have corrected the sentence.

4. p.6 in ‘Stadium and time since diagnosis’, line 5-7: I don’t understand what you want to say.

   We have added an extra part to the sentence:

   A lower mental health over time can arise in cases where longitudinal follow-up resulted in a successful control of HIV. PLWH may then experience difficulties to report mental problems because they are expected to feel fortunate because of their good health [14].
5. p.7, line 2: typo: through
   Ok, thank you.

6. p. 8 in ‘Coping, locus of control, religion’: Internal HLOC and others HLOC would merit some words of explanation.

   We agree and we have added extra information.

   Coping styles are also associated with health locus of control (HLOC). People with an internal HLOC believe that health outcomes result directly from one’s own behaviour whereas people with an HLOC believe that others– other persons, fate, or luck– determine the outcome [57].

7. p.8 in ‘Social support’, line 5: typo: through
   Ok, thank you.

8. p.8 in ‘Social support’: tangible social support would merit some words of explanation.

   We agree and we have added extra information.

   Emotional social support (e.g. empathy, affection, caring) positively influences HRQoL and tangible social support (e.g. financial and material assistance) negatively influences HRQoL.

9. p.9 in ‘Health care, disclosure and stigma’: disclosure was found to have negative effects on physical and mental health. Can you please add the reference(s)?

   Indeed, thank you. We have added the reference.

10. p.9 in ‘Health care, disclosure and stigma’, the last 2 sentences: What do you mean by the ‘obligation’ to disclose? I don’t understand the last sentence: PLWHA should be encouraged to what?

   The formulation has slightly been changed (see below). People may feel obliged to disclose because people ask them about their (visible) symptoms, or about the days they can not go to work etc. They should be prepared to these situations and given courage (e.g. handling self-stigma) by health care providers.

   Disclosing seropositive status was found to have negative effects on both physical and mental health [18]. The latter relationship remains, however, unclear, because disclosure can also be beneficial for the patient’s mental and physical health (mainly through social support) [64]. However it can potentially be related to the fact that people with worse HRQoL have to disclose their seropositive status because of the symptoms, and may feel forced to do so instead of voluntarily doing so.
11. P.9 in ‘Alcohol use’, line 4: you should better explain the statement that light to moderate alcohol use could indicate the ability to engage into riskier behaviour.

    Ok, we agree. We have changed the sentence: *Light to moderate alcohol use could rather be seen as an expression of risk behaviour, for which a certain degree of functional status is required [15].*

12. p.10 in ‘Adherence’: what do you mean by ‘reporting concerns’?

    People who report concerns say that they worry about their medication intakes (e.g. taking the pills discretely, not forgetting to take them...). This may be associated with adherence itself (therefore it is mentioned in that paragraph), however, it is something different.