Author's response to reviews

Title: Physical and emotional health outcomes after 12 months of public-sector ART in the Free State province of South Africa: a longitudinal study using structural equation modelling

Authors:

  Edwin Wouters (edwin.wouters@ua.ac.be)
  Christo Heunis (heunisj.hum@ufs.ac.za)
  Dingie van Rensburg (vrensh.hum@ufs.ac.za)
  Herman Meulemans (herman.meulemans@ua.ac.be)

Version: 2 Date: 28 November 2008

Author's response to reviews: see over
Dear Editor,

PHYSICAL AND EMOTIONAL HEALTH OUTCOMES AFTER 12 MONTHS OF PUBLIC-SECTOR ART IN THE FREE STATE PROVINCE OF SOUTH AFRICA: A LONGITUDINAL STUDY USING STRUCTURAL EQUATION MODELLING

Thank you for the opportunity to revise this article for possible publication in *BMC Public Health*. The amended manuscript reflects the authors’ efforts to address each of the comments and suggestions raised by the reviewers. The remainder of this letter gives specific details of how we addressed each comment, together with the page numbers upon which the relevant changes appear. With the help of an editorial service (International Science Editing), the paper has been re-written with special attention to clarity and brevity. We made the manuscript more appropriate for the average public health reader by describing the methods in simple language.

Comments of the editorial board:

The editorial board believes that the paper is important and deserves publication in *BMC Public Health*. However, it needed substantial revision, incorporating all the changes suggested by the reviewers and most importantly, to make it appropriate for the average public health reader.

1. “Remove ‘a longitudinal study using structural equation modelling’ from the title”
   Page 0: We have complied with this request. The title has been changed to: “Physical and emotional health outcomes after 12 months of public-sector ART in the Free State Province of South Africa.”

2. “Abstract needs to include key findings of SWB in the result section”
   Page 0: The authors have changed the Abstract to comply with this comment. The Results section now clearly indicates that physical QoL had a positive impact on SWB (or emotional QoL) and that the adverse effects of treatment negatively affected SWB.

   “The improved physical and emotional QoL shown at baseline was sustained over the 12-month study period, because treatment duration was not significantly associated with changes in the patients’ QoL. Physical QoL significantly and positively influenced the patients’ emotional QoL (subjective well-being [SWB]) (β = 0.33, P < 0.01). Longitudinal data showed that patients reported significantly fewer adverse effects at follow-up than at baseline (β = −0.38, P < 0.001) and that these adverse effects negatively influenced physical (β = −0.27, P < 0.01) and emotional QoL (β = −0.15, P < 0.05).”
3. “In the methods section, the relevance of mentioning the two surveys of 371 and 307 subjects is not clear, especially because in the analysis only those 268 cases who received ART at baseline are included. The section needs revision and needs to show only relevant information”

Pages 4 and 9: The authors have re-written the Methods section so that it only shows the relevant information. The section describes how the representative sample (of 371 patients) was drawn. This sample included both patients on ART and patients awaiting ART. The section also clearly states that we only included the 268 treatment patients because we wanted to assess the impact of treatment on the QoL of patients. After 12 months of ART, 234 of the 268 patients were re-interviewed. The current version of the article also clearly states the reasons for participant attrition (Page 9).

Page 4: “The sampling frame consisted of a list of names obtained from the Provincial Department of Health of adult patients certified as medically ready to commence ART (CD4 < 200 cells/µL and/or WHO stage IV) within two months of the first patient having received his/her treatment. The list distinguished those patients who were receiving treatment at baseline (‘treatment’ patients) and those who were certified as ready to commence treatment but were not yet receiving it (‘non-treatment’ patients). Eighty patients were sampled randomly from this list for each of the five districts of the province (i.e., Lejweleputswa, Motheo, Thabo Mofutsanyana, Fezile Dabi, and Xhariep), proportional to the number of patients per clinic and per treatment group (treatment and non-treatment patients). Because there were less than 80 eligible patients in Xhariep, a census of all treatment and non-treatment patients was conducted.

A total of 371 study participants were recruited into the study (268 treated and 103 untreated patients). Only patients who were undergoing treatment at baseline (n = 268) were included in this study, because it assesses the impact of ART on the QoL of patients. This study used two waves of panel data to examine the impact of ART on QoL in the medium term. At baseline (< 6 months ART), trained enumerators conducted face-to-face interviews with 268 treatment patients using a standard questionnaire, after the written consent of all the patients had been obtained. Approximately six months later (< 12 months ART), 234 of the original cohort of patients were re-interviewed using an updated version of the questionnaire.”

Page 9: “The attrition rate of 13% (34 patients) between the two interviews was mainly caused by death (n = 15), refusal to be interviewed (n = 8), and our failure to determine the current whereabouts of the patient (n = 5). Attrition analysis of the
study variables (physical and emotional QoL, adverse effects) revealed that responders had significantly better physical and emotional QoL at baseline than those of non-responders and reported fewer adverse effects than did non-responders.”

4. “There is no information about co-treatments (e.g. TB) along with ART among the study subjects that may further influence QoL as compared to those with no co-treatments. In a setting like the Free State, co-treatment with TB drugs, for example, is a common phenomenon that deserves mentioning in the manuscript, including as a limitation if there is no data available.”

Page 13: The possibly disturbing effect of co-treatments was a factor that caused us to exclude from the study those patients awaiting treatment. One of the reasons that these patients were not yet receiving ART is that they had not finished their tuberculosis (TB) treatment. Consequently, none of the 268 patients included in the study was still receiving TB treatment, because the Free State Province requires patients to finish any TB treatment before commencing public-sector ART.

The concern that other co-treatments might have a disturbing effect is a genuine one. Unfortunately, we have no data on treatments for other illnesses received by the patients in this sample. As suggested by the editorial board, we included this limitation in our Discussion section.

“Secondly, although the analysis focused on the impact of treatment duration and adverse effects on physical and emotional QoL, the structural equation model offers an incomplete explanation of the patients’ QoL. Patient characteristics (age, sex) and socio-economic traits (education level and income) were tested as predictors of the patients’ QoL but did not improve the model significantly. Other potentially relevant predictors of QoL (e.g., ART adherence, symptomatic interventions, and co-treatments) were not available in the data set.”

5. “The discussion section should start by highlighting the limitations of the study, which are now at the end of the discussion section.”

The authors agree that the strengths and limitations of the study should be given more attention than in the previous version of the manuscript. This can be achieved in two possible ways. We could move the study limitations to the beginning of the Discussion section or we could place the study limitations in a separate part of the discussion section with its own heading ‘Strengths and limitations’ (as in Pettifor et al., Hauner et al., or Sodergren et al.) [1–3]. We have chosen the latter option.


“Strengths and limitations

The strengths of this study include its longitudinal character and the availability of information on an understudied population. However, it has some limitations. Because of the limited generalizability of the study findings, we can only ascribe the outcomes to patients enrolled in a public-sector ART programme and, more specifically, to patients enrolled in South Africa’s Free State Province ART programme. Secondly, although the analysis focused on the impact of treatment duration and adverse effects on physical and emotional QoL, the structural equation model offers an incomplete explanation of the patients’ QoL. Patient characteristics (age, sex) and socio-economic traits (education level and income) were tested as predictors of the patients’ QoL but did not improve the model significantly. Other potentially relevant predictors of QoL (e.g., ART adherence, symptomatic interventions, and co-treatments) were not available in the data set.”

6. “Authors may consider reducing the reference list”

The authors have reduced the reference list from 73 references to 61 references.

7. “We recommend that you copyedit the paper to improve the style of the written English. If this is not possible, you may need to use a professional copyediting service.”

The revised manuscript was edited by International Science Editing to improve the style of the written English, with special attention to clarity and readability.
**Reviewer Brian G. Williams**

This reviewer considers that the paper is important and should be published (and that it could be published in its original form in a more statistically oriented journal). However, he states that the authors should first add some explanation of the statistics used in the paper. He also feels that, although the authors have defined the question and data collection clearly and their conclusions seem sound and convincing, they should provide more detail in certain areas.

We have complied with this suggestion, and have re-written the statistical sections to improve the readability of the article. The revised version of the paper must also be accessible to a non-statistical audience. Below, we give specific details of how we addressed each comment, citing the page number upon which the relevant change appears.

1. “First of all, I should like to see more of the data included in an appendix or in supporting on-line information. They might for example summarize the responses to the three adverse health effects and to the five generic aspects of current health at baseline and at follow-up. This could be divided by gender and by age group. If the reader is to make a careful judgement of the results, it is essential that they have a better sense of the actual data.”

Page 24: The request for more descriptive information is pertinent. Therefore, we have added a table as an appendix (Table 4), which contains the requested information, so that the reader can make a careful judgement of the results. The table gives a univariate description of the adverse effects of ART, and the physical and emotional QoL at baseline and follow-up. It also shows the bivariate relationships between age and the study variables and between sex and the study variables.

2. “Secondly, the structural equation modelling techniques are familiar to many social scientists but not to few biomedical scientists. They need in the methods section to explain, briefly what structural equation modelling does and why it is appropriate in this case. They then need to explain what is meant by ‘standardized loadings’ (in Table 1, for example) since this will mean little to most biomedical readers of the journal. They never spell out, for example, what is meant by RMSEA and this too needs explanation as does most of Table 1. Table 1 also gives three tests for validity one of which is significant at p < 0.05, the other two of which are not. This needs explanation.”

Various parts of the Methods and the Results sections have been re-written to comply with this pertinent comment. The authors have tried to make the text more suitable for an audience that is not familiar with structural equation modelling.
Firstly, the reviewer asked that some text be added explaining what SEM does and why it is appropriate in this case. In the last paragraph of the Methods section, we have now explained what SEM is and does, and why this technique is especially suitable for longitudinal socio-medical research. In the Results section, we also explain why we used a two-step approach to test the model (first, we tested the measurement model [factor analysis] and then the structural model [factor analysis + path analysis]). We have also added one relevant reference on structural equation modelling techniques.

These changes have been made in the Methods section (pp. 6–7):

“Data analysis

Structural equation modelling (SEM) was used to assess firstly, the influence of ART on physical and emotional QoL, and secondly, the impact of physical QoL on emotional QoL. This model also included the impact of adverse treatment effects on the patients’ physical and emotional QoL. SEM is a combination of factor analysis and path analysis, and is particularly well suited to addressing longitudinal analytical problems. Unlike multiple regression models, SEM permits the simultaneous assessment of multiple dependent variables in a single model. SEM also allows the examination of both the direct and indirect effects of one variable on another. Furthermore, with SEM, a given construct can be treated as both an independent and a dependent variable, providing a model that more closely parallels the complex nature of most social and clinical phenomena (path analysis). Finally, SEM allows the examination of the relationships among both measured and latent variables (factor analysis), which often provides a more precise measure of complex social phenomena than do single measurements [52]. All data analysis was performed with the statistical software package LISREL Version 8.72.”


and the Results section (p. 9):

“Measurement model

Because SEM is a hybrid of factor analysis and path analysis, a two-step approach is recommended. Separate assessments of the measurement and structural models prevent the good fit of one model compensating for (and potentially masking) the poor fit of the other. Table 1 shows the final measurement model, which has acceptable practical fit indices. As in our previous study, the composite reliability
shows the excellent consistency of the indicators in measuring both latent variables: physical and emotional QoL. The discriminant validity of the constructs is supported by the \( \chi^2 \) difference test and the variance extracted test. Combined, these findings support the reliability and validity of the two constructs and their indicators.”

Secondly, the reviewer requested that we explain the concept ‘standardized loadings’, because this was not clear to a broad audience in the original manuscript. As requested, we have added an explanation of this statistical term in Table 1.

Page 21: “The standardized factor loading is the standardized regression coefficient of the latent variable on the indicator (the measured variable). Squaring the factor loading gives us the percentage of variance of the measured variable explained by the latent variable.”

Thirdly, the reviewer requested additional information on the model tests referred to in Table 2 (goodness-of-fit tests, reliability, and validity).

RMSEA is a measure of the discrepancy per degree of freedom of the model. The RMSEA is relatively unaffected by the sample size, and reflects the badness-of-fit per degree of freedom at various levels of model complexity. Mathematically, RMSEA represents the square root of the ratio of the re-scaled non-centrality index (i.e., the population discrepancy function) to the model’s degrees of freedom [1]. In other words, RMSEA is the discrepancy per degree of freedom measured in terms of the population [3] and therefore, is relatively insensitive to the sample size [4]. Browne and Cudeck (1993) suggest that a value of RMSEA of about 0.05 or less indicates a close fit of the model in relation to the degrees of freedom, and a value of about 0.08 or less for RMSEA indicates a reasonable error of approximation.


In Table 2, we have added two sentences explaining the meaning of the RMSEA in such way that a reader unfamiliar with statistical methods can understand its function and use.
Page 22: “RMSEA, root mean square error of approximation. RMSEA is a measure of the discrepancy per degree of freedom for the model and reflects badness-of-fit per degree of freedom. A value for RMSEA of 0.05 or less indicates a close fit of the model in relation to the degrees of freedom.”

Finally, the reviewer also asked us to explain the lack of reference values for the PGFI and PNFI. These fit indices are relative indices, which are adjustments of the GFI and NFI. The adjustments are made to penalize models that are less parsimonious, so that simpler theoretical models are favoured over more complex ones. Although no threshold levels have been recommended for these indices, higher values are preferable [1]. Mulaik et al. (1989) note that it is possible to obtain parsimony fit indices within the 0.40–0.50 region.


The authors have included this information in Table 1.

Page 22: “These fit indices are relative fit indices that are adjustments of the goodness of fit index (GFI) and the normed fit index (NFI). The adjustments are made to penalize the models that are less parsimonious, so that simpler theoretical models are favoured over more complex ones. Although no threshold levels have been recommended for these indices, higher values are preferable.”

3. “Thirdly, the last but one figure can be dropped since it is the same as the last figure without the numbers.”

To comply with this request, the authors decided to delete the second figure as it merely duplicated information. The first figure displays the conceptual model and Table 2 shows the path coefficients.
Reviewer Nigel Livesley

This reviewer requested five minor but essential revisions (“such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct”) and two discretionary revisions (“which are recommendations for improvements but which the author can choose to ignore”).

Minor essential revisions:

1. “The title and abstract mentions outcomes after 12 months of ART but last paragraph in the background states it looks at 6 months follow up and the last paragraph in the Data collection section states 6-12 months. I think it is months 6-12 but I am unsure.”

Pages 0–4: We agree that these different time indicators can confuse the reader. In fact, the patient who had started ART first had been receiving ART for about six months at baseline and for 12 months at the follow-up. Most of the patients interviewed had similar treatment durations. However, a small number of patients had only been receiving treatment for 4.5–5 months at the time of the first interview. We have now changed these different time indicators to ‘less than six months of ART’ and ‘less than 12 months of ART’, because we feel that this definition is both truthful and clear to the reader.

Page 0: “Methods

A stratified random sample of 268 patients undergoing ART was interviewed at baseline (< 6 months ART) and follow-up (< 12 months ART). A model of the relationships between the duration of ART, the adverse effects of medication, and physical and emotional QoL (measured using EUROQOL-5D) was tested using structural equation modelling.”

Page 4: “A total of 371 study participants were recruited into the study (268 treated and 103 untreated patients). Only patients who were undergoing treatment at baseline (n = 268) were included in this study, because it assesses the impact of ART on the QoL of patients. This study used two waves of panel data to examine the impact of ART on QoL in the medium term. At baseline (< 6 months ART), trained enumerators conducted face-to-face interviews with 268 treatment patients using a standard questionnaire, after the written consent of all the patients had been obtained. Approximately six months later (< 12 months ART), 234 of the original cohort of patients were re-interviewed using an updated version of the questionnaire.”

2. “Are the findings described in the Sample Description section from the period 6-12 m or a composite of both time periods? The comparison between findings in months 0-6
and 6-12 could be clearer. I would suggest a table showing the scores on the dimensions of QoL and adverse events in both time periods.”

Pages 8 and 24: This request for more descriptive information is a pertinent one. Firstly, in the previous version of the paper, only the baseline descriptive data were included in the text. In the current version of the paper, we have included the univariate findings from both interviews (baseline and follow-up) to the text in the Sample Description section.

Page 8: “Overall, the patients described their physical QoL as good or excellent, with a relatively small improvement over time. The vast majority of patients had no problems with walking about (81.3% at baseline, 83.2% at follow-up), with washing or dressing themselves (94.0% at baseline, 94.8% at follow-up), or with performing their usual activities (80.6% at baseline, 85.8% at follow-up). Pain and discomfort were more common, and approximately four of every 10 respondents (39.6% at baseline, 37.5% at follow-up) reported at least some pain or discomfort. Generally, the respondents’ emotional QoL was also high: 70.1% of respondents reported no anxiety or depression and 77.6% of respondents were fairly happy to very happy with their life in general, showing high levels of positive affect. The patients’ life satisfaction was slightly lower, insofar as 44.0% of patients were dissatisfied to very dissatisfied with the way their life was going. At follow-up, patients emotional QoL was slightly better: 74.1% of respondents were neither anxious nor depressed, 72.4% were fairly happy to very happy, and only 38.8% were dissatisfied with their life in general.

After six months of ART, 55.1% of patients experienced some adverse effects of the antiretroviral medication. The most reported adverse effects were nausea, skin problems, and dizziness. When we measured the severity of these adverse effects, 58.9% of patients who reported adverse effects experienced them as very disruptive. Approximately six months later, drug substitution and symptomatic treatment had resulted in only 27.3% of patients reporting any adverse effects of treatment. However, 66.7% of these patients experienced these adverse effects as very disruptive.”

Secondly, we have also included a table (Table 4) in the appendix showing the scores for the dimensions of physical and emotional QoL and the adverse events in both time periods. The table also shows the bivariate relationships between age and the study variables and between sex and the study variables.
3. “The median times on ART for each time period would also be helpful especially for interpreting the baseline data. There is a huge difference between months 1-2 on ART and months 5-6. Therefore understanding when the baseline data were collected would be important. This could also go in the suggested table.”

Page 24: To facilitate the interpretation of the baseline data, we have included in Table 4 the median treatment durations at both interviews.

4. “Adverse events decreased over time. The paper states that was due to drug substitution and symptomatic management but provides no data on this. How many people had their drugs substituted? What were the key symptomatic interventions?

Pages 8–9 and 12: Additional analysis showed that 17.7% of patients changed treatments between baseline and follow-up. Of the patients receiving ART, 56.0% started treatment with stavudine, lamivudine, and efavirenz, and 41.8% started treatment with stavudine, lamivudine, and nevirapine. Approximately six months later, 62.3% of patients were using the efavirenz-based regimen and only 36.4% were receiving the nevirapine-based first-line ART. A recent clinical study by van Leth et al. (2005) indicated that both regimens are effective in patients with advanced HIV disease and that any possible differences, if they exist, are small. We have included this information in the Sample Description and have also added a sentence about the proportion of patients who changed treatments in the Discussion section.

Page 13: Unfortunately, there were no data available on the symptomatic interventions used to treat the adverse effects of treatment. The authors agree that this information could potentially contribute to our understanding of the factors that predict the physical and emotional QoL of HIV/AIDS patients on ART. We have now acknowledged this in the Limitations section.

5. “Sample description - typo - ‘pain of discomfort’ should be ‘pain or discomfort’ “

Page 8: The authors have corrected this typing error.

“Pain and discomfort were more common, and approximately four of every 10 respondents (39.6% at baseline, 37.5% at follow-up) reported at least some pain or discomfort.”

Discretionary revisions:

1. “Adverse events are a focus of the paper but the drugs used are not mentioned. They are in the previous papers on this cohort but it would be helpful to include that data here.”
Pages 8–9: The request for more information on the treatment regimens is pertinent. As stated above, this concern has been addressed in the Sample Description section.

“Between baseline and follow-up, 17.7% of the patients changed treatments. Of the patients evaluated, 56.0% started treatment with stavudine, lamivudine, and efavirenz, and 41.8% started treatment with stavudine, lamivudine, and nevirapine. Approximately six months later, 62.3% of patients were using the efavirenz-based regimen and only 36.4% were receiving nevirapine-based first-line ART. A recent clinical study by van Leth et al. (2005) indicated that both regimens are effective in patients with advanced HIV disease and that possible differences, if they exist, are small [53].”


2. “What were the most common disruptive adverse events? (it is surprising that painful feet are not on the list of common adverse events – did they make up a sizable proportion of the disruptive adverse events?)”

Page 12: The most cited adverse effects of treatment were, as mentioned in the text, dizziness, nausea, and skin problems. As requested by the reviewer, we have also considered how many patients reported having painful feet. At baseline 4.9% of patients reported having swollen, painful, lumpy, or cramped feet. Approximately six months later, only 3.4% of patients reported having such problems.

Finally, the reviewer also stated that the article needed some language correction before publication. The authors have taken this criticism to heart and employed the services of an editorial company (International Science Editing) to improve the quality of the written English.