Author's response to reviews

Title: Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: A cross-sectional study

Authors:

Francis L Weng (fweng@barnabashealth.org)
Sheenu Chandwani (chandwsh@sph.rutgers.edu)
Karen M Kurtyka (kurtykkm@sph.rutgers.edu)
Christopher Zacker (christopher.zacker@novartis.com)
Marie A Chisholm-Burns (mchisho3@uthsc.edu)
Kitaw Demissie (demisski@sph.rutgers.edu)

Version: 2 Date: 27 September 2013

Author's response to reviews: see over
September 27, 2013

BMC Nephrology Editorial Team

Dear Editorial Team:

Thank you for the opportunity to revise our manuscript. We appreciate the referees’ careful and detailed comments, and we have revised the manuscript accordingly. We have attached the revised manuscript (R1). In the space below, we address the reviewers’ questions and concerns and highlight our revisions. The referees’ comments are listed in bold font, followed by our responses. New text is indicated by italics.

**Reviewer 1 (Lennerling)**

1. This is a very well written and clear manuscript on an important subject. The results are very interesting, since they show that level of health literacy was not associated with adherence nor lack of knowledge of benefits of immunosuppressive drugs. We thank the reviewer for the compliments regarding our study.

2. I have a few comments and queries…Study limitation not mentioned is the cross-sectional design, this is the same for most studies regarding non-adherence post tx. In this revision, we have added the following paragraph to the end of the Discussion, where we discuss study limitations.

   Finally, we performed a cross-sectional study. This cross-sectional study design precluded meaningful analysis of the associations between adherence and acute rejection. For example, study participants with lower ITAS scores were more likely to have had prior rejection episodes. However, we lacked information on these patients’ adherence and ITAS scores prior to the rejection episodes. An alternative study design would be a prospective cohort study, in which transplant recipients are followed over time. A cohort study would permit correlation of medication adherence with subsequent transplant outcomes, such as rejection or renal function.  (Lines 292-299)

3. **ABSTRACT:** I suggest that you add in methods after ITAS the score 12-0, otherwise the scores in the results make no sense. In the conclusion it is written even among prevalent kidney transplant recipients. What does the word prevalent mean in this context? (I am not a native English speaker but have never seen the word in this kind of context)

   We have revised the following sentence in the Methods part of the Abstract to clarify the scoring of the ITAS.

   We measured self-reported adherence using the Immunosuppressive Therapy Adherence Scale (ITAS, which is scored from 0 to 12, where higher scores indicate increased adherence) and barriers to adherence using the Immunosuppressive Therapy Barriers Scale (ITBS).  (Lines 40-43)

4. **In the conclusion it is written even among prevalent kidney transplant recipients. What does the word prevalent mean in this context? (I am not a native English speaker but have never seen the word in this kind of context)**
“Prevalent” means that we studied existing transplant recipients who had received transplants at some point in the past. Some studies examine only “incident” patients, which in this case would be newly transplanted patients.

5. METHODS in the main text: The participants were given a gift card. This is very unusual and not considered as ethical in some countries even though the sum may be small. I suggest that you describe when this was given. If it was given after the questionnaire were finned in, please add that to the manuscript.
Use of gift cards, as a token of appreciation for study participants’ time, is relatively common practice in the U.S. Use of these gift cards was approved by the human subjects Institutional Review Boards (ethics review) at our institutions, and the amounts were not considered coercive. We have added the following sentence to the Methods:
   After completing the questionnaires, study participants were given a $15 gift card in appreciation of their participation. (Line 107)

6. RESULTS: annual household income < 35000 US dollars. I think you should give some more information on this to guide the International readers.
For reference purposes, the median household income in the United States in 2011 was $50,054. Therefore, an annual household income <$35,000 is lower than most households. We have inserted the following phrase into the relevant sentence of the Results, with a reference to a U.S. Census report:
   28.2% had an annual household income <$35,000 (for comparison, median household income in the United States was $50,054 in 2011) (Lines 165-166)

7. TABLE 1. I would like to see the FEMALEs included in this Table.
The original Table 1 tabulated the number and percentages of males. In our revised Table 1, we have added, on the next line, the number and percentages of females.

Reviewer 2 (Griva)
1. The topic is interesting and clinically relevant yet not particularly novel in terms of focus or methodology. I do believe that studies such as this are important as these broader areas of psychosocial factors (mood, literacy, beliefs) have important effects on the health of transplant patients but authors need to clearly demonstrate how their work adds to existing body of knowledge and understanding.
   We agree that the topic of medication adherence after transplantation is interesting, relevant, and potentially important. In the Discussion, we discuss how our findings regarding barriers to adherence suggest possible targets for future interventions to increase adherence.

2. This study does not seem to provide a strong test of the hypotheses as methodological aspects related to sample and measurement constrain conclusions to be drawn but I believe that it highlights one useful finding, i.e., the comparatively low levels of non-adherence.
   We have changed the Discussion and general terminology to reflect the comparatively low levels of non-adherence.
3. Some problems I noted are as follows…It is difficult to test hypotheses related to
determinants of adherence in a sample of essentially younger and fitter TX recipients
that may not be representative of the TX population. This seriously threatens the
internal validity of results bearing on the factors associated with adherence.
We agree that our study population of prevalent kidney transplant recipients, at a median of
nearly 3 years post-transplant, may not be representative of the general transplant population.
We believe that this may threaten the external validity of our results, in that although the
factors associated with adherence may be true for our prevalent patients, these factors may
not hold true for the transplant population in general. We believe that we frankly discuss
these study limitations in two separate paragraphs of the Discussion (Lines 268-286).

4. Volunteer bias was significant, including a large proportion of people who refused or
were unable to participate. The authors need to clarify what and comment on
representativeness of the study sample. A substantial number of patients screened were
not approached due to clinical concerns. It is also no clear what ‘clinical concerns refer
to’. Were these patients that were not eligible due to clinical inclusion criteria? The
authors need to explain.
We agree that volunteer (selection) bias was likely significant. At the time of clinic visits,
patients often had clinical concerns (e.g. fever, worsening allograft function, or other acute
illness) that were the focus of the visits. Therefore, these patients were often not approached,
despite being possibly eligible. To clarify, we have revised the following sentence of the
Results:
The remaining screened patients were not approached, due to clinical concerns *(e.g. acute
illness)* at the time of the office visit. (Lines 161-162)
Our Discussion section also has a full paragraph (Lines 275-286) that explicitly mentions that
our study is limited by selection bias in its study subjects.

5. Why categorise adherence based on these cut offs? Were these established cut offs?
Categorization constrains variability and introduces the threat of classification errors
that, again, threaten the validity of results. It would be useful for authors to comment
on their approach.
The ITAS has been used on other studies, but cut-offs for its 12-point scale have not been
established. Given that the majority of study participants had an ITAS score of 12 (the
highest score possible, corresponding to better adherence), we felt that for the analysis,
categorization of the ITAS to permit logistic regression would be more useful and
interpretable than using the raw ITAS score and linear regression. We agree, however, that
this approach constrains variability. We have added the following full paragraph to the
Discussion section, where we delineate study limitations:
Second, we categorized adherence using cut-off scores for the ITAS. Although the ITAS
itself has been validated, these cut-offs and categories of ITAS scores have not been
validated for their association with outcomes. The clinical significance of different ITAS
scores and categories is uncertain. To our knowledge, the correlation between specific
amounts of adherence (whether measured on the ITAS or other instruments) and post-
transplant outcomes remains unknown. (Lines 262-267)
6. It would be useful to add data on clinical profile of patients (e.g. medical regime, immunosuppressant type and serum concentrations). Were the patients classified as non adherent, outside clinical targets for serum concentrations of immunosuppressants?

We did not collect data on serum concentrations of the immunosuppressants. We do have data on which immunosuppressant our patients used, which we have included at the end of our revised Table 1.

Reviewer 3 (Howell)

1. The number of acute rejection episodes differs significantly between the ITAS score groups - however no further assessment in relation to non-adherence.

In this study, we reviewed patients’ medical records to determine the occurrence of prior acute rejection episodes. We did not further assess the relationship of non-adherence with this rejection, given that our assessments of non-adherence occurred after any episodes of rejection noted in the medical record. We have added the following to the Discussion of limitations:

Finally, we performed a cross-sectional study. This cross-sectional study design precluded meaningful analysis of the associations between adherence and acute rejection. For example, study participants with lower ITAS scores were more likely to have had prior rejection episodes. However, we lacked information on these patients’ adherence and ITAS scores prior to the rejection episodes... (Lines 292-296)

2. The clinical significance of the ITAS score should be discussed. Much is made in the discussion of the large proportion of patients with some level of non adherence whereas 85% had a score >9. The authors should consider the clinical significance of this level of non adherence. The assessment may be that there is no evidence, however this is an important aspect of the evaluation of the results and associated uncertainties.

We agree that the clinical significance of the ITAS score is uncertain. Cut-offs for the ITAS have not been validated. As mentioned above (Reviewer 2, #5), we have inserted an entire paragraph in our revised Discussion to address the uncertain clinical significance of low ITAS scores.

We also emphasize that the original purpose of this study was not to determine cutoffs of adherence that are associated with clinical outcomes. Instead, we were interested in determining risk factors for non-adherence and barriers to adherence.

3. The discussion has been written to place an emphasis on their being a high level of non-adherence by using words such as 'substantial'. However, 85% of the patients had an ITAS score >9. This is not necessarily a helpful approach and it would be better to place an emphasis on the study showing the majority are adherent or have minor deviation and then to discuss the clinical relevance.

We have revised the manuscript to change this emphasis. The first sentence of the Discussion (Lines 226-228) now states:

In this cross-sectional study of prevalent adult recipients of kidney transplants, most patients were very adherent with their medications, at least by self-report. A minority of patients reported non-adherent medication-taking behaviors.

The second paragraph of the Discussion now states:
Our results confirm that a notable minority of kidney transplant recipients are non-adherent with their prescribed medications. (Lines 234-235)

We also revised the Conclusion of the Abstract, which now states:

Among prevalent kidney transplant recipients, a minority is non-adherent.

4. The basis for assessment of the ITBS scores is the correlation with ITAS and this is reported as an odds ratio. Correlation is to be expected as the ITBS is also a measure of non-adherence given that it is likely that an adherent individual would identify few if any barriers. It might be helpful to tabulate the ITBS scores so that the relative importance of each of the barriers can be seen.

We have added a new Table 3 that tabulates the responses to significant individual items within the ITBS. We reference this Table 3 in our Results (Line 212), where we discuss barriers to adherence. This new Table 3 permits the reader to see the relative importance of each barrier. The numbering of the subsequent table has been updated.

5. In the discussion it is stated that interventions aimed at addressing psychosocial factors are unlikely to have a appreciable impact on non-adherence. In my view given the limitations of this study (as stated by the authors) this statement is not supported. There is a high prevalence of depression in kidney transplant recipients and depression has been associated with poor outcomes as well as non-adherence and there are available interventions for depression that should not be discounted. This is particularly so given that addressing non-adherence is a multi-factorial problem that likely involves a high level of individual counseling and tailoring of interventions in addition to broader strategies.

Given the Reviewer’s concerns, we have deleted that entire paragraph in the Discussion.

6. Is the question posed by the authors well defined? Yes, however as it is a cross sectional study and does not address the clinical significance of non-adherence as measured by the self-report ITAS instrument the question is of limited additional value given the current state of knowledge. The prevalence and risk factors for non-adherence has been the subject of many cross-sectional studies and reviews and what is lacking are well designed prospective studies and analysis of the clinical significance of non-adherence as measured by self-report instruments such as ITAS. For example the clinical significance of unintentional non-adherence (i.e. missing doses from time to time) which represents the majority, is unknown. The clinical significance of ITAS scores should be discussed and as necessary noted as a limitation of the study.

We agree with the reviewer that prospective studies are needed and that the clinical significance of unintentional non-adherence requires further study. To our knowledge, “thresholds” of adherence associated with better and worse outcomes have not been documented for transplant recipients. We agree that the clinical significance of ITAS scores is unclear and is a study limitation. We have added portions to the Discussion to address this (see response to Reviewer 2, #5).

7. Are the methods appropriate and well described? Yes with the following exceptions. • As noted above, the clinical significance of the ITAS scores has not been discussed. •
There does not appear to have been a sample calculation performed. • The exclusion of screened patients on “clinical concerns” is not described in the methods section. We have addressed the exclusion of screened patients on “clinical concerns” (see Reviewer 2, #4).

8. Are the data sound? Yes, however the following comment is provided for consideration:
   • Table 1 indicates the number of acute rejection episodes to differ significantly between the ITAS scores. However, this has not been noted in the text and no further analysis has been undertaken. This is a short coming given the possible association between acute rejection and non-adherence and also with depression and anxiety. • ITAS and ITBS should correlate given that the ITBS is essentially also a measure of non-adherence – that is if someone is adherent, they are unlikely to identify barriers. In my view ITBS should be used as a basis for identifying the most common barriers rather than associations with the ITAS score. It might be more useful to provide data in a form other than ORs for association with ITAS of 9 or lower.
   As mentioned in point #1 for this reviewer, we did not further analyze rejection episodes, given that they occurred in the past. We also provided more information on the ITBS responses and barriers, in our new Table 3. This Table provides frequencies and percentages, not just odds ratios.

9. Does the manuscript adhere to the relevant standards for reporting and data deposition? Generally yes, however as noted above it is unclear why acute rejection has not been evaluated.
   See response to point #1.

10. The discussion and abstract have been written in such a way as to emphasise a high proportion of patients were non-adherent through the use of terms such as ‘substantial’. However, 85% of the participants had an ITAS score of 10 and greater and the clinical significance of this level of deviation from medication adherence has not been addressed and is probably unknown. Stating that 40% had non-adherence of one form or another is of limited value in the absence of an evaluation of clinical significance.
   We agree. See response to this reviewer’s point #3 above.

11. The study cannot provide a basis for concluding that psychosocial factors may not necessarily increase medication adherence as it may well be under powered to show the associations and is a highly selected sample (as noted in the limitations). Given the consistent evidence for associations between social support, depression and anxiety and non-adherence they should not be dismissed (on the basis of this study) as likely to be of limited value in interventions to address non-adherence. The prevalence of depression in transplant recipients is high and there are effective treatments.
   See response to this reviewer’s point #5.

12. The meaning of the following statement: “Our results confirm that a large proportion of kidney transplant recipients are non-adherent with their
prescribed medications, even in a population that was a median of nearly three years post-transplant."is unclear. Time since transplantation has been shown in other studies to be a risk factor for non-adherence, so it is unclear as to the point being made by reference to three years post-transplant.

Our study population had had a functioning transplant for a median of almost 3 years. Our point in that sentence is that the study participants had to be somewhat adherent, given that their transplants had survived a median of almost 3 years. We agree that other studies have shown that increased time since transplant is associated with worse adherence. We have deleted the confusing clause, so that sentence now reads:

Our results confirm that a notable minority of kidney transplant recipients are non-adherent with their prescribed medications. (Lines 234-235)

13. Are limitations of the work clearly stated? Generally yes. • The study being cross-sectional and of a select population is consistent with current understanding and does not provide a basis for identifying causal factors or potential effectiveness of interventions. • The clinical significance of non-adherence has not been evaluated.

We agree that we have stated the limitations of the work, including its cross-sectional nature (Lines 292-299).

**Conclusion**

We again thank the editors, for the opportunity to revise our manuscript, as well as the referees, for their thoughtful reviews. We respectfully submit that we have addressed the referees’ questions and concerns, either in this response letter or in the revised manuscript.

We would be happy to address any other additional concerns regarding our manuscript, and we look forward to hearing from you.

Sincerely,

Francis L. Weng, MD, MSCE
Email: fweng@barnabashealth.org
(On behalf of Sheenu Chandwani, Karen Kurtyka, Christopher Zacker, Marie Chisholm-Burns, and Kitaw Demissie)