Author's response to reviews

Title: Individual and Contextual Factors of Influence on Adherence to Antiretrovirals Among People Attending Public Clinics in Rio de Janeiro, Brazil

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Version: 2 Date: 27 April 2013

Author's response to reviews: see over
Authors’ Response to Reviews

Title: Individual and Contextual Factors of Influence on Adherence to Antiretrovirals Among People Attending Public Clinics in Rio de Janeiro, Brazil

Version: 2
Date: 26 April 2013

Authors’ response to reviews is below. We feel the manuscript is improved due to the new revisions.

Reviewer’s report
Title: Individual and Contextual Factors of Influence on Adherence to Antiretrovirals Among People Attending Public Clinics in Rio de Janeiro, Brazil
Version: 1 Date: 5 March 2013
Reviewer: Michael Scanlon

Reviewer’s report:
Reviewer’s Report

MAJOR COMPULSORY REVISIONS
Introduction
None
Methods
1. In paragraph 1, you state that this analysis is part of a larger study. Please include who is directing this research, funding the research and whether any previous publications have resulted from the study.

The study was coordinated by Francisco I. Bastos (Oswaldo Cruz Foundation), funded by the Ford Foundation and a former paper addressed some comparative results between its findings on the field of sexual and reproductive health and some findings from the Johns Hopkins OB/GYN clinics coordinated by Dr. Jean Anderson.

The reference is as follows:

2. In paragraph 3, a few points deserve attention:
a. You state that a pilot test was conducted to ensure clarity. What methods were used? Cognitive interviewing? Focus groups?
b. Please clarify that the methods described in the rest of the paragraph apply to
the pilot study, main study or both? It is confusing and as it reads now sounds like the paragraph is describing the methods of the pilot study.

Focus groups were conducted in each clinic before launching the survey. This information and further clarifications have been added.

Measures
None
Analytic strategy
None
Results
None
Discussion
1. In paragraph 6, you discuss the concept of social capital but don’t provide any citations. Please provide relevant sources. Additionally, a small body of research does exist on the relationship between HIV and social capital in resource-limited settings. Please consider including some of these references in your discussion.

Reference was added. While there is some interesting work on social capital and HIV, a lot of work is focused on the bonding component and does not capture the argument in the discussion about the importance of bridging, especially because resources might be limited on the horizontal level.

Tables
1. Table 1. For “Partner HIV Positive”, please give justification for why the entire sample was included (n=632) in this breakdown when only n=307 identified having a partner. This seems like an error to include the entire sample here.

We wanted to include an indicator that would capture disclosure and possibly support from another HIV positive partner. Therefore those who had an HIV positive partner were included and all others were coded as 0.

MINOR ESSENTIAL REVISIONS
Introduction
1. In paragraph 2, the following sentences are a bit misleading:
“While almost perfect adherence to the complex regimen is required to maintain viral suppression, the average rate of adherence to ARVs is only 70 percent in developed countries. (12,13) A recent meta-analysis found an average rate of adherence to ARVS at 62% worldwide.”(14)
Earlier you state that adherence levels have been found to be similar in resource-poor and resource-rich settings, however, the two sentences quoted above make it appear resource-limited settings have significantly less adherence. Given the sources, I would suggest combining these sentences or just referring to the meta-analysis (14), since it is 10 years more recent than the other studies (12,13) and adherence often declines over time.
The more recent meta-analysis was kept.

2. In paragraph 2, you state the following:
“Adherence to ARVS has become an important area of research because it is a strong predictor for progression to AIDS; furthermore, adherence can be improved through carefully planned interventions.” (3,13)
This statement seems too strong given the body of evidence on improving adherence to ARVs through interventions. True, there are a few studies that show improvements in adherence with interventions (eg adherence education/counseling, reminders like SMS), but the body of evidence is often conflicting and inconsistent, especially for interventions in low and middle-income settings. I would consider revising this sentence to more accurately reflect the available data on adherence interventions and their limitations. (See Scanlon, ML and Vreeman, RC “Current strategies for improving access and adherence to ARVS in resource-limited settings.”

The language was adjusted to “may be improved” and references documenting further advances in this field were included.


3. In paragraph 3, you state the following:
“Sociodemographic variables have not been shown to consistently predict ARV or other medication adherence; (18,19) though being male, white, older, having higher income and higher literacy have been associated with better adherence.” (20)
First, these two statements are contradictory. Second, are the associated factors (being male, white, older, having higher income and literacy) you cite consistently associated with adherence? In what settings? You only cite one study to support this statement. I would provide more evidence, clarify what setting and reword this sentence to not be contradictory.

The citation was not a study but an article synthesizing factors associated with adherence. Additional current references were added and the sentence was revised.

Methods
1. It would be very helpful to further define a “public health clinic” from which your
sample is drawn. You say these are run by the Rio de Janeiro Health Secretariat, so they are government run. Are these HIV care specific clinics? Are they primary care clinics? Are services provided for free? Insurance required? Are ARVs provided for free? Are all clinics within Rio proper? Urban/rural? Largest vs smallest caseload included (to better explain the heterogeneous inclusion). Answering a few more of these questions would provide readers a better idea of where the sample accesses treatment and services provided.

All clinics included in this study are secondary level clinics, which provide care for many different conditions above a primary care clinic. All services are free, including all medications for AIDS and medicines included in the popular pharmacy program (i.e. medicines provided at no cost for chronic conditions such as diabetes and hypertension). Insurance is not required. All the clinics are located in the urban area of the municipality of Rio. Caseloads are heterogeneous and the sampling strategy was adjusted accordingly, with large sampling quotas for clinics with larger caseloads.

Measures
1. Under socio-demographic and background variables – please clarify what you mean by “main partner status?” Does this mean married, single? HIV status?

This refers to their relationship status, whether they have a main steady partner.

Results
None

Discussion
1. In paragraph 2, the vulnerability of women to HIV and negative HIV-related outcomes is discussed. I would consider addressing issues of challenges/barriers in access to ARVs in female populations here as well, as you don’t mention this point. Added “Women might also experience challenges in accessing ARVs due to lack of knowledge, stigma and discrimination.”

2. In paragraph 4 discussing the pattern of the HIV epidemic in Brazil, it is not clear why you are able to draw the conclusion that HIV starts in higher income populations and disseminates into poorer populations. Your examples supporting this claim are not clear. If there is strong evidence to support this claim that account for different demographic and risk factors in southeastern versus northeastern populations, please clarify.

These trends are not from our own data but from many different papers documenting these trends in Brazil, such as the following:

Dourado I, Milroy CA, Mello MA, Ferraro GA, Castro-Lima Filho H, Guimarães


3. Nowhere in your discussion do you mention the concept and impact of HIV related stigma. There is a lot of research on how stigma may impact adherence to ARVs, especially in resource-limited settings. It may be appropriate to mention the potential impact of HIV stigma on adherence, perhaps especially relevant for women. A small discussion of HIV stigma may be most relevant in paragraph 5 when you discuss social support, as HIV stigma can greatly reduce the options for accessing support networks.
Discussion of stigma was included.

Limitations
1. Please consider also including a brief discussion on generalizability of these results in Brazil and other resource-limited settings. Might there be some important differences in the sample population compared to other key populations of interest?

The findings from this study come from regular clinics, where most Brazilians access care across the different regions, and not referral centers, where most of the studies in Brazil are conducted. Therefore these findings are more generalizable than other studies in Brazil but since Rio de Janeiro is the second largest city in Brazil, these findings should not be generalized to either poorer areas inside Brazil or low-income countries.

Tables
1. Table 1. Please correct the symbol under “Number of children” from >=2 to the standard #2
2. Table 2. Please revise this table to increase clarity and simplicity. I would suggest the univariate analyses to the left and multivariate analyses on the right-most column. I do not see a need for the unadjusted OR if you only cite adjusted OR in the manuscript.
UOR are also sited in the manuscript. It is also good to see how stable the OR are across the analysis.
DISCRETIONARY REVISIONS
Introduction
1. Consider reorganizing the introduction section to create a more logical flow. To do this, I recommend first discussing ARVs and the research on factors of adherence. Then go into your discussion of Brazil as a case study and specific research on populations in Brazil. As written, the introduction is choppy and bounces back and forth between Brazil and more general topics. The first paragraph introduces why it is important to examine ARV adherence in Brazil. Then there is a general discussion of the literature on adherence which then focuses specifically on the Brazilian literature.

2. In paragraph 4, you state the following: “The variables found to be important are similar to those previously discussed, including a combination of patient, medication and clinic level factors.” Nowhere previously are medication and clinic level factors discussed in the manuscript, only patient level factors, so this statement is a bit confusing. The variables discussed was referring to the previous paragraph discussing the adherence literature. The additional variables mentioned was in reference in the Brazil data that was then discussed (so they wouldn’t be mentioned earlier).

3. In paragraph 4, you state the following: “Another study in Rio had high self-reported adherence at 82 percent, with self-efficacy, sexual orientation, loss of appetite and the doctor-patient relationship found to be significantly associated with adherence.”(7) It would increase clarity to note what sexual orientation and aspects of doctor-patient relationship were associated with adherence in this study.

Methods
1. In paragraph 2, you state the following: “These six facilities provide care for approximately 60 percent of the over 14,000 patients living with HIV/AIDS under follow-up” Please consider clarify what you mean by “under follow-up.” Under follow-up by the public health clinics?
Receiving follow-up care.
Results
1. In paragraph 1, you use the term “superior level.” I would refrain from using this term and simply use “university level or higher” for clarity.
Changed.
2. In paragraph 1, you state that the monthly income ranged from 0 to 4,790 USD with a mean of 530 USD. Given the range and low mean, I would suggest using the median value here instead of mean to give a more accurate representation of monthly income.
Changed.
3. In paragraph 2, you state the “only 17% missed a dose on the weekend.” Is this 17% of the entire sample reported missing a dose on the weekend? Is this 17% of the nonadherent sample that reported missing a dose on the weekend? I would clarify this finding.
The findings were presented for the entire sample and clarifications were made.

4. In paragraph 3, you state that gender was associated with adherence in bivariate analysis. I would suggest stating what association was found – “Being a male was associated with adherence.” Even though you do this in your multivariate discussion, I would also do it here.

Discussion
None

Limitations
None

Tables
1. Table 1. I would consider using different terminology to describe “Non-white.” You describe “Non-white” as “black, brown, yellow and indigenous.” I understand that this is the official terminology of the Brazilian Institute of Geography and Statistics, but to some this language might seem odd and out of date. It is also unclear to me why you only classified race between white and non-white, instead of white, black and brown.

We were capturing the effect of being white versus other instead of the nuances between brown and black. The IBGE terminology may be outdated but it was used in the last census (2010) and used to define policies for employment and education in country.

American racial/ethnic criteria have been explicitly rejected by researchers, policy-makers and the general public in Brazil, as discussed in the paper as follows (among many others):


The categories were renamed to White vs Nonwhite (Black, Brown, and Other).

2. Table 1. I would consider using different terminology to describe the highest education level. I would substitute the phrase “superior or more” to “university level or more” if this accurately reflects your classification.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report

Title: Individual and Contextual Factors of Influence on Adherence to Antiretrovirals Among People Attending Public Clinics in Rio de Janeiro, Brazil

Version: 1 Date: 6 March 2013

Reviewer: Mariana Hacker

Reviewer's report:

Discretionary Revisions

1. One discussion of the study is the role of caretaking and number of children on adherence, it would be interesting to test if the association between adherence and number of children is heterogeneous according to gender categories. It wasn’t significant in the bivariate and the study was not powered for gender stratification.

- Minor Essential Revisions

1. In the abstract, provide the period of study. Added.

2. In methods section, explain about the recruitment process and the distribution of participants across the selected clinics. According to caseload. The greater the caseload, the greater number of participants sampled from the clinic.

3. In first paragraph of results, change the term “population” to participants or respondents. Changed.

4. In results, (2nd paragraph) it was said that adherence was significantly correlated with viral load, but the coefficient was 0.22. If it is a linear correlation, this value is considered low to show a correlation. There are more factors than viral load that would explain adherence such as resistance. The correlation was significant and the association held in the bivariate.

5. In last paragraph of page 9, rephrase the sentences: “Those with high social support were significantly associated with adherence than those with low social support (AOR 2.85 CI [1.50-5.41]). Of the economic factors, having a high asset index was positively associated with adherence than a low index (AOR 2.47 CI [1.79-3.40])."

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Reviewer's report

Title: Individual and Contextual Factors of Influence on Adherence to Antiretrovirals Among People Attending Public Clinics in Rio de Janeiro, Brazil

Version: 1 Date: 15 March 2013

Reviewer: Inge Corless

Reviewer's report:

Review of “Individual and Contextual Factors of Influence on Adherence to
Antiretrovirals - - - - “
This is a generally well-written paper, a pleasure to read.
What follows are so comments and questions all of which should be addressed or I wouldn’t have mentioned them.
1. Abstract: Background- You mention multiple settings and populations and then state you need to consider the “particularities of that context”. Why is it one context? If it’s contexts please add the s. If you’re saying something different please clarify.
   Changed to “each context.”

2. Abstract: Background- The last sentence of your background sounds like a conclusion. What you’re trying to do is explore these relationships.
   Changed to “This research explored ARV adherence and individual, relational and environmental-structural factors.”

3. Abstract: Methods- How did you define a “complete” file? Please explicate. All files that do not have missing observations. Less than 3 percent were dropped.

4. Abstract: Results- Why did you use four days when many studies use the past three days? You make comparison more difficult.
   There are many ways of measuring adherence and we used the AIDS Clinical Trial Group’s (ACTG) standard.

5. Abstract: Results- Your data indicate it’s one child and not at least one child that’s associated with adherence. With more than one child this relationship didn’t obtain.
   Corrected.

6. Abstract: Results- Why did you make gender and environmental-structural variable. It’s more typically considered a socio-demographic variable. You will need to expand on this decision in your paper.
   We conceptualized gender as a structural variable that would affect adherence. Just as income might be measured at the individual level, it can be conceptualized as a structural variable. It is not the biological sex variable that we’re interested in but what being a woman captures as part of living with HIV in Brazil.

7. Abstract: Conclusions- Your statement of conclusions doesn’t provide any new information.
8. Introduction: P. 3: Roll out should be roll-out.
   Changed.
9. Methods: Participants and procedures- Here again you mention complete case participants as your sample. You need to inform the reader as to how this was defined.
10. Methods: Participants and procedures- Paragraph 2- “under follow-up”, more felicitous phrasing would be “receiving follow-up.” Changed to “receiving follow-up.”

11. Methods: You don’t mention compensation for the time of your participants. Was this not provided? No compensation was provided.

12. Results: P.8 and Table 1- Many of the % are more than 100%. Why is this? There was an error with the excel sheet that has been corrected.

13. Results: P.9- Length of time on ARV’s- you have someone who has been on ARV’s for 23 years which given data collection was completed in 2009 would mean that the individual started ARVs in 1986. Do you have a record of this? It appears most unusual. This was self reported and it is possible given AZT has been distributed in Brazil since the very beginning of the dissemination of the first results published in the US, around this period. In that period there was no national initiative to provide AZT on a regular basis (which happened only after 1988), but many people got it through litigations.

14. Results: P.9 In your discussion of Table 2 you mention significant associations for two or more children, high education as being significant. The Table doesn’t reflect this. Bivariate associations were considered significant with p-values less than .10.

15. Results: P.9 Why did you decide to include depression in further analyses given it was not significant. You need to provide a rationale. As stated in the analytic strategy, “nonsignificant variables hypothesized to be confounders or effect modifiers based on findings from previous research, or included for conceptual purposes.” Depression and anxiety were clinical relevant and there was a high prevalence in the context of many different chronic conditions.

16. Results: P.9-10 (last paragraph)- The presentation of these findings is awkward and needs to be rephrased.

17. Discussion: P.10. Paragraph 3. The following sentence seems incorrect” WE found that having at least one child was associated with being adherent - - - “ You found that having “only one child” was what was statistically significant. Corrected.

18. Discussion: P11- you make this same assertion again. It needs to be corrected. Corrected.

19. Discussion: P12- Why do you think anxiety and depression were not
significant in your final model? Such associations may be easily confounded by other clinical (e.g. profound immunodeficiency and/or anemia) and social factors (poverty, lack of social support). Once controlled by other variables putatively associated with such other outcomes, the original associations may not remain significant.

20. Where do you show your final model with the explanatory factors for adherence? Table 2 has the final model under AOR.

21. Conclusions: P13- Second sentence- adherence was negatively associated with women – not the way you phrased. It. I'm not sure about this distinction. The independent variables are associated with the outcome.

22. Your references tend to be old and while this may be understandable for the review of the literature, it is not acceptable for a paper that is being reviewed in 2013. New references were included.