Author's response to reviews

Title: Contrasting predictors of poor adherence to antiretroviral therapy in two South African treatment programmes: a cohort study

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Author's response to reviews: see over
Response to reviewers’ comments

Title: Contrasting predictors of poor adherence to antiretroviral therapy in two South African treatment programmes: a cohort study

Version: 2

Reviewer: Paula Braitstein

Methods

Comment 1 – Major essential if possible
“Participants were referred to the study by clinic staff and we do not have information on the number of people starting ART in the clinic who were eligible for the study but refused referral.” Do you at least have number of people starting ART in the clinic who were eligible? This would enable at least a basic comparison to elucidate any referral bias that may have existed. (Major essential if possible)

Response to comment 1
During the study period approximately 550 patients were started on ART in the community programme and 216 in the workplace programme. However, we do not know how many of those started on ART were actually eligible for the study (at least 18 years of age and ART naive). Since clinic staff reported few refusals for study referral we suspect that the majority of those not referred were not informed about the study.

We agree that the suggested comparison between those enrolled and the general patient population enrolled during the study period would informative. As below we have included a comparison of age and gender between the two populations (See results section, page 9, paragraph 1).

During the study period the total number of patients who started ART, irrespective of whether or not they met the study eligibility criteria, was 550 in the community and 216 in the workplace. Among this population 267 and 144 participants were enrolled onto the study in the community and the workplace, respectively. The gender and age profiles of the general patient population and of the study cohort were similar. In the community, 64% of the general population were female compared to 61% of study participants, while the median age among the general population was 38 years compared to 37.5 years among participants. In the workplace, 4.6% of the total population were female compared to 4.5% among those enrolled, while the median age in both groups was 46 years.

Comment 2 - Discretionary
“Refusal to provide this information [follow-up contact information] was not an exclusion criterion.” Did you consider this refusal as a co-variate? Perhaps a marker of stigma/disclosure issues. (Discretionary)
Response to comment 2
Among those eligible for the study and offered study participation none refused to provide contact information. The following sentence was added to the results section, page 9, paragraph 2

All participants agreed to provide contact information for tracing in case they missed the six months visit.

Comment 3- Discretionary
A comparison of those excluded vs. those included would be helpful (Discretionary)

Response to comment 3
We agree with the suggestion. The results section (page 9, paragraph 3) was amended to read as follows:

Characteristics of the 227 community and 117 workplace participants included in the risk factor analysis are shown in Table 1. In the community programme the median age was 37 years (interquartile range [IQR]:31-44), the majority were female (67%) and unemployed (71%). This was despite a median duration in education of 11 years (IQR:8-12). The median CD4 count at ART start was 101 cells/mm$^3$. The 40 individuals in the community programme excluded from the risk factor analysis were similar in age (median 38 years) and educational level (median 11 years) to those included, but were less likely to be female (47%) and had a lower baseline CD4 count (median 66 cells/mm$^3$). In the workplace, only six (5.1%) were female. The median age was 46 years (IQR:37-52) and median duration in education was seven years (IQR:3-9), and median CD4 count was a 183 cells/mm$^3$. The 27 individuals excluded from the risk factor analysis were similar to those included in age (median 47 years), sex (none female), educational level (median 4 years) and baseline CD4 count (median 162 cells/mm$^3$).

Comment 4- Discretionary
Did you ask about toxicity/side effects and the impact of those on either adherence or treatment outcomes? (Discretionary)

Response to comment 4
The main aim of the paper was to see if those with poor treatment outcomes could be identified before the start of treatment with a view to providing extra adherence support from the start. Thus adverse effects after start of treatment were not a focus of enquiry. However, we did ask whether participants had fears of experiencing side effects once they started ART. This variable was not related to poor outcomes.

Comment 5- Minor essential
What were the ART eligibility criteria in each of the programs? (Minor essential)

Response to comment 5
Medical eligibility was added to the setting section in page 5, paragraph 1 of the manuscript.

In the community: Individuals were medically eligible for ART if they were in WHO stage 4 and/or had a CD4 count of <200 cells/mm$^3$. 
In the workplace: Individuals were medically eligible for ART if they were in WHO stage 4; or had a CD4 count of <250 cells/mm³; or were in WHO stage 3 with a CD4 count<350cells/mm³.

Discussion

Comment 6 – Major essential
Given that the outcomes and predictors of them varied so much between the two programs, can we, and if so what and how, generalize from these findings? What can the rest of Africa learn from these data? (Major essential).

Response to comment 6
In the manuscript we highlight the differences between the two programmes and how these differences could inform similar programmes in low-income countries. Specifically we theorize that this difference reflects the potential for the community programme to have a primarily self-selected and hence more motivated and adherent patient population, among whom structural factors are the main barriers to adherence and subsequent success on treatment. In contrast, the workplace programme potentially extended ART to a “second generation” [23-24] of patients who, without the active promotion of provider-initiated testing and referral for treatment, may have been less motivated to spontaneously self-present for these services. In this second generation of potentially less-well motivated patients we can hypothesise that individual-level beliefs of ART efficacy may play a larger role in determining adherence than structural barriers critical among those who seek out treatment more spontaneously in the community programme. Among individuals entering care through provider-initiated testing and referral, there may be a need for more robust adherence support focused not only on ameliorating structural barriers to succeeding on treatment, but also on addressing alternative beliefs of HIV and its treatment.

The following paragraph was amended in the conclusion section (see page 15, paragraph 2) to better highlight the main lessons learned.

In the workplace and similar programmes in lower income-countries, where provider-initiated testing extends ART to individuals potentially less motivated to seek care, patients may need additional adherence support especially addressing uncertainty about the health benefits of ART and how to maintain adherence even if they elect to seek complementary methods of treatment. Meanwhile, in the community programme and in others that are similarly less focused on provider-initiated testing, efforts to improve adherence and retention should continue to focus on addressing structural barriers and on increasing access to ART to those currently unable to receive treatment.

Comment 7 – Minor essential
“Dissatisfaction with programme services was associated with poor adherence in both programmes.”
The definition of adherence should be in the methods, not the limitations part of the discussion. (Minor essential)
Response to comment 7
The sentence incorrectly refers to adherence rather than treatment outcomes. The sentence has been corrected to read as follows: (see page 10, paragraph 3)

*Dissatisfaction with programme services was associated with poor treatment outcomes in both programmes.*

Comment 8 – Minor essential
Were the questionnaires used identical in the community and the workplace programs? (Minor essential)

Response to comment 8
Yes the questionnaire used in both sites was identical. The following sentence was amended in the study procedures section: page 6, paragraph 1:

*At baseline, a semi-structured questionnaire lasting approximately 45 minutes was conducted with participants at both sites to assess exposures potentially predictive of poor adherence.*

Comment 9- Discretionary
“It also may have reflected the surprisingly prevalent scepticism regarding the existence of HIV altogether [19], which could in part relate to lower levels of education or the rural origin of many employees, where alternative beliefs in disease causation may be more robust than in urban areas.” I find nothing surprising about the prevalence of this scepticism given that this study takes place in South Africa. (Discretionary).

Response to comment 9
We agree that there have been widespread reports about scepticism regarding HIV and its origins in South Africa, especially among political leaders. However, there are not many studies in South Africa or elsewhere that describes these beliefs among patients already on ART. Additionally, the prevalence of these beliefs was far less prevalent in the community programme compared to the workplace programme, despite them both being in South Africa.

Comment 10- Major essential
“Participants were referred to the study by clinic staff and we do not have information on the number of people starting ART in the clinic who were eligible for the study but refused referral. Therefore, we cannot be certain that the prevalence of specific characteristics, or the proportion with poor treatment outcome, is representative of all patients in the clinic who were eligible for the study.” Same comment as above about looking at the basic characteristics of the main cohorts to identify any potential referral bias. (Major essential)

Response to comment 10
Agree. See response to comment 1
Tables:

Comment 11- Discretionary
Table 2: Very difficult to read because it is so big. Suggest you break it up into Table 2a, 2b, 2c, and 2d to represent distal, intermediate, proximal, and biological variables. (Discretionary)

Response to comment 11
We could break up the table if the editors agree it would help the final format of the manuscript.

Comment 12: Discretionary
I would highly recommend a table for the multivariable models. (Discretionary)

Response to comment 12
The multivariable models are shown in table 3. The exposure variables included in the final models are shown table 3; all the variables assessed, subdivided by distal / intermediate / proximal, are shown in table 2.
References


12. Logistic Regression with Stata [http://www.ats.ucla.edu/stat/stata/webbooks/logistic/]


