Author’s response to reviews

Title: What happens to ART-eligible patients who do not start ART? Dropout between screening and ART initiation: a cohort study in Karonga, Malawi

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Responses to reviewers’ comments for MS: 5439470563869991

Dear Dr Aldcroft,

Thank you for inviting us to resubmit a revised paper to your BMC Public Health journal. We are grateful to the four reviewers for their insightful comments and suggestions for improving the paper.

We have edited the paper to extend the methods, places where the writing style was too general, and clarified or removed other sentences noted by the reviewers. Our responses to comments are addressed below.

REVIEWER 1 COMMENTS

1) Method section. Second paragraph. Socio-demographic and clinical data. Please explain in more details which information was requested and which variables will be explored in the analysis. What do the authors mean by “treatment outcome”? It becomes clear in the result section that this is death, but should be clarify at this point. How was the death status ascertained? From reporting of relatives?

Response: The methods section has been expanded to include a statistical analysis section and an appendix has been provided that indicates the clinical data collected at the screening visit. We have also clarified the text that the primary outcome of interest was whether each ART-eligible individual started ART. Among those who dropped out before starting ART, we investigated why they had dropped out. Death was one reported reason by household informants. To avoid misunderstanding, we do not use the term ‘treatment outcome’ in the revised paper, and have clarified that deaths were reported by relatives to staff at the clinics or during tracking visits.

2) In the introduction, it is stated that individuals were eligible for ART in Malawi if they were assessed to be in stage III/IV or stage II with a CD4<250 cells/mm3. However, in the Karonga District Hospital no CD4 tests were available and eligibility to ART initiation was determined only using WHO stage. The authors should discuss whether having information on CD4 could have been helpful in this study to identify sicker patients and if these results are generalisable to the other clinics in Malawi where CD4 testing was available. Furthermore, in footnote in table 1 says that “Six had low CD4 count recorded”. This contradicts the statement that CD4 tests were not available at the hospital laboratory. Please clarify.
Response: We have now clarified in the results section that ‘Six hundred and thirty-three (633/730, 86.7%) were told they were clinically eligible for treatment (Figure 1), including six individuals who were in WHO stage II but had a CD4 count<250 cells/mm\(^3\) established through their participation in a KPS research study’. We have also added the following text to our discussion ‘Previous work by our group has suggested that ART eligibility based on clinical staging criteria alone may miss up to two-thirds of those considered eligible using criteria based on clinical staging and CD4 cell count and highlighted a need for simpler CD4 testing methods. However, in countries with constrained resources, and increasing decentralisation of services, the current available technologies make it unlikely that CD4 testing will be available in small health centres that are now integral to ART programmes. Where equipment is available and CD4 testing is a policy, challenges remain in ensuring no interruptions in the supply of reagents, power supply and trained technicians. In many aspects the ART Clinic in Karonga operated like any other district ART clinic in Malawi, characteristic of the simplified public health approach established by the Malawi Ministry of Health, furthermore outcomes of those who started ART at Karonga were also similar to those reported from other clinics thus we expect that the results of this study can be generalised to other clinics in similar contexts’.

3) Method section and Table 1. Please clarify how the final multivariable model in Table 1 was obtained (eg, step-wise selection, etc). For instance, why occupation and BMI were not included in the final model?

Response: This has been addressed by adding a statistical analysis section to the Methods section.

4) It is not clear how the variable timing of ART initiation was classified and the first 2 categories overlap. Did the authors mean 0-7 days, 8-30 days, +31 days, for instance? If so, why did you choose these categories?

Response: The labeling of this variable in the table has been clarified and the following has been added to the statistical section ‘A separate set of indicators was used to represent whether an ART initiation appointment was given to the ART-eligible individual for 0-7 days, 8-30 days or 31+ days after their screening visit. These categories were chosen to reflect the target of giving ART initiation appointments within a week of screening, vs a delay in the appointment date and splitting that into less than or more than 1 month’.

5) Discussion. First sentence: “biasing outcome” not clear. Which bias and which outcome?

Response: This sentence has now been changed to ‘The phenomenon of dropout after screening has been well documented with respect to TB treatment but less well examined in HIV treatment. Exclusion from analysis of TB patients who die or are lost between presentation and starting treatment has been shown to potentially bias programme estimates of TB outcomes, making them difficult to interpret and potentially misleading’.

6) Were there children included in the study? If so, how many? If so, is it reasonable to use age<30 as the lower age category?

Response: We have included in the results the following ‘The median age of the participants at first presentation was 36.7 years, (IQR 30.9 – 44.3), with 9 <18 years old (median 14.9,
range 13.3-15.8 years). These 9 individuals were too few in number to include as a separate category.

7) Pag 8. The sentence “The significant positive association between drop out and length of delay from screening to the initiation appointment is consistent with a Cambodian study that showed higher loss to follow-up in early years of the ART programme when access to ART limited” is not clear and would benefit from rewording.

Response: This sentence has been clarified.

8) Introduction: add cells/mm3 after CD4count<250.

Response: This has been added.

9) Pag 6. Second paragraph of the Result section. "A composite indicator of any report of difficulty with activities ... age or sex". Is this the variable "disabilities" in Table1? If so, this should be stated more clearly in the footnote of the table.

Response: This has been included in the statistical section of the methods, and the labeling has been changed in the table.

10) The authors conclude that MUAC & difficulty in dressing could be used to identify sicker patients. However, wouldn't be more recommendable to prioritise treatment initiation based on WHO stage and/or CD4 at enrollement? Did the authors expect to find no role of WHO stage?

Response: We have included the following text in the discussion ‘In a context where CD4 counts are not available, MUAC and reported difficulties in dressing may provide useful screening indicators to identify sicker ART-eligible individuals who may benefit from priority ART initiation when waiting lists exist, or admission to hospital. The finding that WHO stage IV was not associated with the odds of dropout before ART initiation compared to those in WHO stage III was unexpected. This may reflect the specific policy of keeping some appointments each week ‘open’ for sicker patients, or represent an increased effort by individuals to seek treatment because they were sicker’.

REVIEWER 2 COMMENTS

1) I think this paper needs reorganisation; for example:
# Introduction: The 3rd and 4th sentences of the introduction actually describe the methods and should therefore be put under methods i.e. 3rd sentence starting with “individuals were eligible for ART in Malawi………” and the 4th sentence starting with “ideally, the group counselling session………”
# Methods: I think the first paragraph of the methods would fit better under the introduction
# Second paragraph of Methods: The 1st and 2nd sentences are actually results and should therefore be put under results
# Conclusion: 1st and 2nd sentences should be put under introduction

Response: We have reorganized the Introduction and Method sections as suggested by this reviewer. We now explain both the Malawi national ART programme and the Karonga ART clinic in the Introduction, and have kept the methods focused on study related details.
2) Methods:
# The method of this study has not come out clearly. I think it is important for the authors to mention clearly what happens during each visit e.g. what happens during a screening visit; what happens in the subsequent visits; how long were patients’ appointments etc?

Response: This has been added.

# My understanding is that, all eligible patients (who did not have any contraindications) were actually given appointment to come back to start ART (though the length of these appointments varied from a few days to over a month); what determined that a patient is scheduled to come back after 2 days and another one scheduled to come back after 1 month for example (was it just the length of the waiting list alone?)

Response: We have added in the introduction ‘Ideally the group counselling session occurred 2-3 days after staging, with ART initiation one week later. However, this varied depending on the length of the waiting list. Two appointments a week were kept ‘open’ to fast track individuals who were very sick but deemed stable enough to initiate immediately’.

3) Results
# 1st sentence: Definitions of “readiness to start treatment” and “contraindications” should be given. These should in fact be put under methods e.g. the authors could state “… a patient was not considered ready to start treatment if he/she had ……..” “….. A patient had a contraindication if he had e.g. a severe drug reaction with previous treatment, or was pregnant……..”

Response: We have added to the methods ‘A clinician staged each individual’s HIV disease and, if ART-eligible, assessed their readiness to start treatment based on their understanding of the treatment benefits, willingness to adhere and to continue even if they felt better, and their ability to attend the clinic regularly (in terms of costs, that they lived in the district etc).. Some individuals were considered ART-eligible, however they were too sick to start immediately and needed to be stabilized before starting ART. Others had medical contraindications and were told to come back later; either they were taking rifampicin (i.e. were in the intensive phase of TB treatment, this has since changed as a recommendation), ketaconazole or were in the first trimester of pregnancy’.

4) Conclusion:
# The conclusion/recommendation of this study is not clear to me. The objective of this study was to measure extend of loss of ART-eligible individuals between screening for ART and initiation of ART, and to identify factors associated with this loss. Some of the key findings are a high default rate and a high death rate among eligible patients who were not started on ART. Based on these, it is therefore not clear to me how considering the use of “eligible for ART as a denominator” becomes a conclusion. Using “eligible for ART” is not the focus of this paper, is it? I think the authors would do well to maintain the focus of this paper just by asking simple questions: what did we set to measure; what did we find; based on these findings, what can we conclude; and based on these findings, what recommendations can we make?

Response: We have clarified this by rewording the conclusions ‘ART programme success is currently judged on the basis of the proportion of those who start ART who survive and continue to receive ART. However we have shown that there are many patients who are
considered eligible for ART, but do not receive it. We also show that a major reason for not receiving ART is that they die. These early deaths are not included in routine programme statistics. Considering all those who are eligible for ART as a denominator for programme indicators would help to highlight this vulnerable group, in order to identify new opportunities for further improving ART programmes’.

5) # The authors do not need to bring again other people’s work in the conclusions. They can mention other people’s work in introduction/background, methods and discussions. I therefore think, references 14 and 15 that appear in the conclusion should be removed and taken somewhere else.

Response: We have corrected this.

6) Understanding reasons for defaulting from the patients’ perspectives in such a study is critically important in order to draw a more plausible conclusion. Therefore, in addition to the quantitative study, I think the authors would have achieved more if they had also done a qualitative study to further explore e.g. the reasons for defaulting among patients who are eligible but not started on ART.

Response: The tracking team explored the reasons for defaulting during the home-visits. Paragraph 5 of the results summarises the reasons.

7) Did the authors miss anything by focussing only on the patients who dropped out? I know their aim was to determine extend of dropout and find the reasons associated with dropout. But how different was this group that dropped out from the other that did not; how different were the delays for those who dropped out from those who remained in care. For example, the authors found an alarmingly high death rate among patients who were not started on ART immediately. One would naturally ask, was this death rate really high; or one would ask, compared to what? I think the authors need to show: a) how different this death rate is compared to death rate among the peers that were started on ART; b) through a verbal autopsy, what the causes of death were in order to determine whether they were HIV-related deaths. In other words, to what extent can we attribute these deaths to delay in starting treatment or dropout from ART. After finding a positive association between dropout and length of delay to start treatment, the authors would have done even a better job by looking at the group that were started on treatment; did they also have a similar length of delay and if they did, what was their motivation to remain in care etc

Response: We have clarified in the paper that this analysis focuses on the period up to the start of ART and aims to highlight that many of those who don’t start ART have not come back to clinic because they have died. Unfortunately, verbal autopsies were not available for these pre-ART deaths.

8) Discussion
# Paragraph 2, 1st sentence: statement beginning with “MUAC and difficulties in dressing……….” I think the issue here is not inability to identify sicker individuals. The patients were already identified as eligible for ART (using the existing criteria) and scheduled to come back for (possibly) ART preparation and then initiation. The patients did not come back and the question then should be why? Even then, further validation of such a tool (difficulties in dressing in particular) needs to be done before making such a recommendation.
Response: We have addressed this in our response to reviewer 1, point number 2.

**REVIEWER 3 COMMENTS**

Introduction

- Please provide background information for this population, i.e., yearly incidence, prevalence and mortality associated with HIV.

Response: In Malawi, adult HIV prevalence has stabilised at about 14% since the late 1990s[1]. Before antiretroviral therapy became available, in June 2005, mortality in adults (aged 15–59 years) in Karonga district was estimated to be 9·8 deaths per 1000 person-years.

Methods

- In the sentences “No CD4 tests were available at the hospital laboratory. Therefore, eligibility was usually determined using WHO stage.” The word usually is confusion, if not CD4 eligibility or WHO stage, what else did you use for eligibility?

Response: The word ‘usually’ has been removed and it has been clarified that the number ART-eligible included ‘six individuals who were in WHO stage II but had a CD4 count<250 cells/mm3 established through their participation in a KPS research study’

- What sort of questions were asked in the interview?

Response: Details of the variables available and the clinical questions asked have been added in the methods and as an appendix.

- Did the regimen provided to all these individuals contain stavudine plus lamivudine plus nevirapine?

Response: We have included the following text in the Introduction ‘A generic, fixed-dose combination treatment (Triommune) with stavudine, lamivudine and nevirapine is available as first line treatment and given free of charge to eligible patients. An alternative first line treatment option is available if an individual has unacceptable side effects to Triommune. Second line treatment is available if an individual is considered to have failed first line treatment’.

- Please describe (and define is appropriate) which socio-demographic and clinical information were gathered in these individuals. Assuming that you have more than one possible factor to make into your multivariable model, how did you select the final model? This is an explanatory model, please mention this as well.

Response: This has been included in the statistical section added to the methods

- How does this clinic compare with other ones in the region?

Response: This has been addressed in our response to reviewer 1, point number 2.

Results
• In the first sentence, you mentioned between parenthesis the numbers 13 and 4, please rewrite using N=13 and N=4. It gets confusing with the style of references in this paper.

Response: These have been changed.

• In the third sentence in the first paragraph, how late is late? What is the median (IQR) follow-up time that people started ART at a later time?

Response: We have added to the results ‘In addition, 13 of the 17 clinically eligible participants initially advised not to start treatment started later (Figure 1), a median of 22 days (IQR 13-27 days) after the screening visit’.

• If a patient had a contraindication to treatment, what happen to this patient?

Response: The specific contraindications have now been clarified in the paper. Some contraindications were transient and the patient was allowed to start ART once treatment was no longer contraindicated.

• The table is quite messy. Please re-organize it.

Response: The table has been reorganized.

• You mentioned the univariable model results. I would drop it and mentioned the distribution of the population regarding the different factors. Then, I would go directly to the multivariable results.

Response: This suggestion has been incorporated into the text of the results section.

• In the education, please situate the grades with the western world. It is easier to make comparisons like this.

Response: We have added to the Methods ‘Malawi’s education system provides 8 years of primary and 4 years of secondary school. Students may study in any of the three major local languages for most of the first 4 years of primary school after which English becomes the medium. Thus, for our models we grouped individuals who had no schooling, those with 1-4 years of primary education, those with 5+ years of primary education but never attended secondary school, and those who attended at least one year of secondary or continued through further education’.

• Define acronyms used in the text, table and figure.

Response: This has been addressed.

• How many people died without assessing ART?

Response: In paragraph 5 of the results we clarify ‘We tracked 60 (65%) of these at home, a median 55 days after they had missed their ART appointment (IQR: 35, 83). Thirty-five (58%) had died, 21 before their ART initiation appointment and the others soon after (median 19 days after appointment, IQR 7, 47)’.
• Please revise the grammar.

Response: This has been addressed.

• Do you have demographic information on the individuals that you have not included in this study? How different were they in comparison to the ones included in the study?

Response: We do not have any demographic information on the individuals who were not included in the study.

Discussion
• This paper is missing on the policy implications of the results.
• Most of your conclusions do not fit with the data provided. Please re-write it.

Response: We have addressed this in response to reviewer 2, point number 4.

REVIEWER 4 COMMENTS

Methods
1. In the Methods, it would be helpful to describe the protocol for dealing with patients who are ineligible for ART at the screening visit, since this group is discussed in detail later.

Response: We have now included this in the methods ‘For individuals who were told that they were not yet clinically eligible on the first visit, clinicians would make appointments if they wanted to review the person again, otherwise they were asked to return when they had symptoms.’. We have also added a 2nd figure to complement the text in paragraph 4 of the results regarding outcomes among those who were not clinically eligible at the first screening visit.

2. In the Methods, can you describe what clinical information was obtained at baseline in greater details? For example, are other data collected either routinely at the screening or specifically by the study that have been shown in other studies to predict poorer outcome (such as hemoglobin, albumin, tuberculosis, etc)? Also, please describe CED and its measurement in this section.

Response: Details of the data available, and the definitions used in the analyses have been added to the methods section, and the clinical questions have been included as an appendix.

3. Were standardized/validated tools used to measure functional status (called “Disability” in the table) or other baseline measurements? If so, please describe and cite these here.

Response: The following has been added to the statistical section ‘The questions asking about difficulties in daily living were based on self-care and mobility questions from the activities and participation domains section of the WHO International Classification of Functioning, Disability and Health. Initially, each question was considered in the analysis using a separate indicator to represent functioning (any difficulty vs no difficulty) in a particular activity. In addition, a composite indicator was created to represent reported difficulty in any activity vs no reported difficulties’.

Results:
4. The authors offer an interpretation in the results section as to why people screened earlier would be more likely to be seen during the study period than those screened later. I would favor putting interpretation into the discussion. It is not self-evident to me that those screened earlier in the study would be more likely to be seen again. One could argue that while the clinic staff was new and less-experienced, more patients would be lost. One could argue that patients enrolled later would have had a shorter period of follow-up and therefore less of an opportunity to be defined as lost. In any case, I would not offer this interpretation in the results section.

Response: We have moved our interpretation from the results section and included the following in the discussion section ‘The finding that participants enrolled in the later calendar periods of the study had a significantly higher odds of dropout compared to those recruited in the earliest period of the study may be due to particularly motivated patients coming for screening as soon as the clinic opened’.

5. Along those lines, can you put a median duration of follow-up in the results section?

Response: We have not included this because we no longer refer to follow-up period (see previous response).

6. The concluding paragraphs of the results section includes patients who came back for subsequent screening visits. Again, this needs to be mentioned in the methods section. 60 patients were tracked to their homes; why were the other 33 not sought in the community?

Response: We have clarified the procedure for subsequent screening visits and for tracking in the Methods section. In the results section, we have clarified ‘Twenty one (64%) of the 33 not sought in the community had ART initiation appointments after mid-June 2006, i.e. shortly before the end of the study’.

7. Figure 1 puts an emphasis on patients who started ART, while the patients who did not return are off to the side and do not have a surrounding box. I think because the paper is about patients who dropout, these patients should be emphasized.

Response: We have summarized the findings of why people dropped out in paragraph 5 of the results section.

Discussion:

8. An important result of this paper is that delay from screening visit to ART initiation appointment is a major predictor of patient dropout (HR 5). Delay to appointments and the role of waiting lists and other clinic/program characteristics that lead to delays should be discussed and put into context with other work in the field.

Response: We have added the following to the Discussion ‘Now that the service is well established, delays between screening and starting treatment are no longer a prominent feature. This is likely to change if criteria are altered to enable people to start treatment at an earlier stage, and may require a two-stream service to ensure that those in more clinical need are not affected by waiting lists’.
9. While the number of patients is small, an additional important finding is that several ART-eligible patients alive and in the community cited lack of a suitable guardian/buddy as a barrier to ART. This would benefit from some discussion; what evidence is there that a guardian/buddy improves outcomes? Does this remain a requirement for ART in the Malawi system today?

Response: We have added the following to the discussion ‘Several ART-eligible patients alive at the tracking visit cited lack of a suitable guardian/buddy as a barrier to ART. The policy of requiring a guardian to accompany individuals until they are established on ART remains part of the national programme in Malawi. This policy is based on experience of the national TB treatment programme and its impact has not been formally evaluated in the ART programme. In a society where literacy and education levels are low, a guardian also receives the treatment-related education and can support the individual, remind them to take drugs, help with drug taking, attend clinic on their behalf etc. In Malawi, hospital patients are expected to come with a guardian to provide basic nursing care – washing, feeding, toiletting etc. In the ART programme context, guardians can also provide physical help to get to clinic, and care whilst at the clinic’.

10. Similarly, financial and transport barriers should be put into the context of other related work in Africa on this topic.

Response: We have expanded the text in the discussion and included references on this topic from Malawi. ‘Among those found alive at a home visit, the most frequent reported barrier to returning to the clinic was cost of transport, a barrier that has also been documented in centralised PMTCT and ART programmes elsewhere in rural Malawi[20,22]. These reports suggest that targeted support may be beneficial at screening visits but poverty-related barriers are likely to be persistent and also affect long-term retention on ART. More recent devolvement of ART initiation from the district hospital alone to additional rural hospitals within the district, resulting in shorter distances for individuals to attend an ART clinic is likely to have eased this barrier’.

11. The conclusion that ‘eligible for ART’ should be a denominator for programme indicators is a sound one, but I think this idea could be fleshed out a little bit. Doing so would put a new emphasis on getting ART-eligible patients onto treatment, would help identify barriers within the individual program and within the Ministry of Health, and would potentially lead to a greater financial investment in this vulnerable time for patients.

Response: We have addressed this in response to reviewer 2, point number 4.

Results

12. In Table 1, the heading “% of N not seen” is confusing? Is this % of N who dropped off? Please use consistent terminology to indicate patients who were lost prior to ART initiation.

Response: This has been clarified.

13. It appears that “difficulty in dressing” is a sub-item from the “disability” item in Table 1 and should be listed immediately below “disability”. Is “disability” a measure of functional status? If so, I think that would be a more appropriate heading.

Response: This has been addressed in the table and clarified in the statistical section of the methods.
We also provide a copy of the questions used to collect clinical data at screening visits in the Karonga ART clinic, as requested, for an appendix. We would like to add the following as a footnote to the appendix: “The findings section of this form was developed as a clinical tool / checklist of symptoms and signs to lead the clinician systematically through all the AIDS defining criteria when ascertaining ART eligibility. In this district, in common with most areas of Malawi, diagnostic facilities are limited and it is not possible to obtain microbiological, histological or imaging support for WHO Stage 4 diagnoses”.

We look forward to your response.

Yours sincerely,

Nuala McGrath