PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adherence to antiretroviral drug therapy in adult HIV-positive patients in Northwest Ethiopia: a study protocol.
AUTHORS	Bezabhe, Woldesellassie; Peterson, Gregory; Bereznicki, Luke; Chalmers, Leanne; Gee, Peter

VERSION 1 - REVIEW

REVIEWER	Makonnen, Eyasu Addis Ababa University , Department of Pharmacology
REVIEW RETURNED	08-Aug-2013

THE STUDY	The language and formatting need to be fixed. Some of the references, especially Reports are not cited in the correct style.
RESULTS & CONCLUSIONS	This is the protocol of a study; no results are included in this manuscript.
GENERAL COMMENTS	Title: 'adherence to' rather than 'adherence with' Make it clear in the title and/or aims that this is a protocol, not the results paper Abstract Page 1, line 20 – 'achievement of optimal treatment/medication adherence' Under key message it is mentioned that the study duration is 16 months. This does not match with information on page 1 of the abstract under 'methods and analysis'. Be consistent in the use of tense in the paper. Introduction Line 29: 'achievement of optimal treatment/medication adherence' Page 4, line 10 - ADRs, 'and' fluid and dietary Page 4, line 38: do you mean with a longer follow-up? The objectives should clearly state that it is about 'medication adherence' Methods & Analysis Line 9: You don't need to say 'prospective longitudinal cohort study'; 'prospective cohort study' should be enough Lines 25- 29: How will you measure depression, stigma, knowledge etc? Using validated scales? Why "Data's"?? Information about the nested qualitative study should be added to the first sentence about the study design (line 9). Fig 1: what data will be collected at 4 months? this information is currently missing It is unclear to me why measures are different at different follow-up points. Some explanation/justification for this is required.

	Based on piloting how long does it take for participants to complete the questionnaire? The Methods section requires better structuring. Design, setting, inclusion/exclusion criteria, recruitment, data collection, Sample size, analysis, ethics…… Study setting rather than 'implemented' use 'carried out' Some additional information about the hospitals will be useful. How many beds, how many HIV/AIDS patients per year attend this hospital, what is the population in the catchment? The sample size won't be adequate if the authors want to do multivariable analysis using the various scale items as independent variables. Given that the 'recruitment' period is already over that information needs to be written in the past tense. PC is not a common abbreviation; suggest giving it in full "Adherence to medication found using multiple measures would be converted in to percentage of dose adherence and triangulated". This requires further explanation with the help of an example, if possible. "The optimal level of adherence in this study will be taking 95% or more of the dispensed ART regimen at a point in time." Are you referring to MPR or pill count? What is the likely impact of 'Hawthorne effect' on your results? Why viral load/CD4 count are not used as surrogates of adherence? Page 12, line 17: 'patients not presenting for refilling their' "Study subjects who do not make at least 6 months follow-up will be excluded from the study." These are non-persistent patients and I think it will be useful to look at their characteristics separately and comparing with those who are nonadherent. Lines 26 & 33: 'lost to follow-up' instead of 'lost from follow-up' Line 35 – delete 'Analysis of' Data Anlaysis Do you mean 'chi-squared test for comparing proportions and independent sample t-tests for comparing continuous data that follow normal distribution'. Para 1 on page 14 needs to be rewritten. 'strengths/limitations of the study' rather than 'strength/limitation' Under Ethics and Dissemination – include information on 'written informed consent' Funding - None However, I notice that participants will be reimbursed for their time/travel Reviewer's Competing interests: In the past I have held joint grants

	and publications with some of the authors of this manuscript. However, these have been on topics different to the subject of the current paper. There are a few typographical and formatting errors, which need to be fixed.

REVIEWER	Damen Haile Mariam Professor of Public Health & Health Economics Addis Ababa University Ethiopia.
REVIEW RETURNED	28-Aug-2013

THE STUDY	Abstract: At least, it is not appropriate to claim the study as the first of its kind conducted in the country to identify factors that affect adherence to ART. Introduction: I am not sure if the authors have adequately reviewed the local literature to claim that there are no studies that looked at barriers to, and facilitators of adherence to antiretroviral therapy (ART) in the Ethiopian setting", I think there are a couple of studies that have made follow ups (even though not prospective) on the issue and the authors have not come across them. Objectives: I am not sure whether the patients from the two hospitals would be representative of the patient population within the whole country to claim about "factors in Ethiopian patients".
RESULTS & CONCLUSIONS	Results: As the manuscript is rather a research proposal, it does not have any results at the moment.
REPORTING & ETHICS	I am not sure if the current national guidelines would allow this type of study to go ahead without approval by the National Ethical Committee. The authors are not also following a consistent referencing style.
GENERAL COMMENTS	I do not know the policy of the journal (BMJ Open). Otherwise, the manuscript is rather a research proposal and I do not think it is worth considering publishing it at this stage. The authors do not also seem to have exhaustively reviewed the literature on relevant studies at local level.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Johnson George
The language, tense, formatting, typographical and reference errors were fixed.
Abstract and Key message:
1. Title: It has now been corrected to "adherence to" and "a study protocol" has been added to the title to indicate the paper is a study protocol.
2. Page 1-line 20: it has now been corrected to "achievement of optimal medication adherence"
3. Key message: The duration "16 months" was corrected to "12 months"; it now matches the duration mentioned in the methods and analysis section of the abstract.
Introduction:
1. Line 29: corrected to: "achievement of optimal medication adherence"
2. Page 4, Line 10: 'and' inserted.
3. Page 4, line 38: yes, I do mean a longer follow-up. (Now fixed)

Objective:
I have inserted “medication adherence” instead of “adherence”
Methods and Analysis:
Line 9: Corrected to “prospective cohort study”
Line 25-29: We are measuring these factors using validated scales. Depression is measured using 7 items of the Center for Epidemiological Studies-Depression (CES_D) scale, Berger stigma scale (10 items), HIV treatment knowledge scale (21 items), …
“Data” instead of Data’s corrected.
Line 9 study design: The qualitative study is a sub study to help to identify the unique factors influencing adherence in these settings, it has been designed and carried out separately, not part of the cohort. Semi-structured interview and focus group discussion are used to explore the factors that facilitate or hinder adherence to ART. The study involves adherent patients, patients lost to follow-up, and nurses and peer counselors working in ART clinics from the two hospitals. I have taken out the previous information “We have also designed a separate qualitative study to be conducted side by side involving patients taking ART, and nurses and peer counsellors working in ART clinics to help to explore the unique factors that affect adherence in these settings.” regarding the qualitative study from the manuscript.
Fig 1: “ADR interview”. ADR data are collected at month 4 (it was not visible- now unhidden)
Why measures are different at different follow-up points? The questionnaires have been spread to track changes of the different parameters over time as shown in figure 1, while minimising questionnaire fatigue. On average it took about 23 minutes for participants to complete the questionnaires at each appointment date.
Method section:
The methodology section has been structured: Study design, Study setting, Inclusion/exclusion criteria, Sample size, Recruitment, Measures, Statistical analysis, Quality control, Data management, Ethics and dissemination and Conclusion.
Study setting:
“Carried out” used instead of “implemented”
Additional information:
Each hospital has 400 beds and serves a catchment area of 5 million people. The number of total HIV/AIDS patients attending each hospital is around 7,000 and 10,000 in Gondar University Hospital and Felege-Hiwot Hospital, respectively. This information has been added to the manuscript.
Sample size:
This is good information. This could be one of the limitations our study we did not involve large number of study participants to minimise the costs needed to carried out the study.
The steps that have already occurred have been changed to the past tense.
The abbreviation PC is now replaced with pill count in all documents.
Triangulation:
The self-report method overestimates adherence by up to 20%. Although suitable for routine clinical practice, this is not sufficiently accurate for the trial setting thus triangulating it with the pill count method will be useful for validation of the ability of self-report to estimate true adherence in the setting.
In our study, self-reported percentage adherence over 30 days will be triangulated with percentage dose adherence obtained using pill count over the same duration, which will be useful to estimate patients’ true medication adherence.
The optimal level of adherence has been measured using pill count, as pill count is more reliable.
Hawthorne effects on our results and possible way to minimise are incorporated in the manuscript:
The multiple measures of adherence used in the study may alter patients’ behaviour and overestimate medication adherence (i.e. Hawthorne effect)(44). The data collection points coinciding with the patients’ clinic appointments, not representing additional contact with healthcare providers to minimize the Hawthorne effect on adherence.
CD4 count as a surrogate marker:

Biological surrogate markers such as viral load and CD4 count correlate with medication adherence(24). The CD4 count is measured every 6 months in ART clinics; the measures at months 6 and 12 will be used as a biological surrogate marker of adherence. Viral load is not routinely measured in Ethiopian clinical practice so has not been included in the trial protocol.
Page 12, line 17:
I have accepted your suggestion; the characteristics of non-persistent and persistent patients will be compared instead of excluding patients who attended the clinic for less than 6 months.
Line 26 and 33: I have corrected to “lost to follow-up”
Line 35: “Analysis of” was deleted.
Yes, chi-squared test will be used to look at the association of categorical variables (measured using nominal and ordinal scales), independent samples t-tests will be used to analyse continuous data that follow the normal distribution.
The following information taken from consent added:
Nurses working in the ART clinics familiarised patients with the study; research pharmacists delivered further information to interested participants. Participants were given the chance to read and understand the information sheet and to ask any questions before providing written consent. Copies of the information sheet and consent form were handed on to study participants who consented. All personally identifying information has been removed from the questionnaires and study documents. Study participants have been identified only using a unique study number.
Para 1 on Page 14: This section is now rewritten.
“Strength/limitation” is now corrected to “Strengths /limitations”
Funding: The Tasmanian School of Pharmacy, University of Tasmania, supports the study.

Reviewer 2: Prof. Damen Haile Mariam
Abstract and Introduction:
I have accepted your suggestion it was not appropriate to claim, “the first of its kind conducted in the country” as there may be prospective studies that we were not able to locate in the international literature. I have been modified the sentence to “This study will identify factors that affect adherence to ART in treatment naïve patients who are initiated on ART with long-term follow-up.”

It is true that there have been a number of studies carried out in Ethiopia to identify factors associated with adherence; we have also come across these studies. However, most of them have been cross-sectional in their design. I have cited the prospective study of 3 months duration conducted in adults taking ART in southwest Ethiopia by Amberbir et al. (Amberbir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health. 2008;8(1):265). What makes our study diferent is that it will be conducted for a year and therefore offer a much longer follow up period. I have also seen a prospective study on adherence to ART in pediatric patients in Ethiopia (Mirkuzie et al. Current status of medication adherence and infant follow up in the prevention of mother to child HIV transmission programme in Addis Ababa: a cohort study) but it is likely that the factors associated with non-adherence will differ between adults and children.

Objectives: I have accepted your suggestion and modifed the title of the protocol to indicate that the study is being conducted in Northwest Ethiopia. It may not therefore represent the whole Ethiopian population.
I am not sure to what extent the ethics review bodies at diferent levels in the country are working with the demarcation given to them. The Institutional Ethics Review Committees have previously provided ethics approval for such types of research.
The referencing style was reviewed and corrected.
The following paragraph is taken from BMJ Open about the importance of publishing study protocols.
“Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help

prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study."
We therefore believe that our manuscript will be of interest to the readers of BMJ Open.