Author's response to reviews

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

Authors:

Mison Dahab (maysoon@mdahab.com)
Salome Charalambous (scharalambous@auruminstitute.org)
Alan S Karstaedt (karstaedt@mweb.co.za)
Robin O Hamilton (rohamilton@auruminstitute.org)
Katherine L Fielding (katherine.fielding@lshtm.ac.uk)
Lettie LaGrange (llagrange@Angloplat.com)
Gavin J Churchyard (gchurchyard@auruminstitute.org)
Alison D Grant (alison.grant@lshtm.ac.uk)

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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

Authors: Dahab M et al.

Version: 1

Reviewer: Amita Gupta

Major compulsory revisions:

Comment 1
1. The authors define adherence in a different way than what has been traditionally used as the definition in other published literature. Specifically they define non-adherence as either a detectable viral load >400 c/ml at 6 months or discontinuation of care and treatment at 6 months verified by active tracing. Typically most published papers have used medication adherence either by validated self-report questionnaires or pill count methods. The authors are correct to say that viral load is often used to validate adherence measures. Since they report collecting adherence to medications at both 6 weeks and 6 month visits, it would be useful to assure the reader that use of viral load in this study was strongly correlated with adherence to medication. This is because lack of adherence is a key reason for detectable VL but it is not the only reason (prior exposure to ART even if thought to be ARV naive, transmitted resistance etc). Perhaps the authors should reframe their study description to state baseline factors associated with detectable viral load at 6 months and failure to continue in care.

Response to comment 1
As suggested, we have reframed the outcome definition from poor adherence to poor treatment outcomes, encompassing both detectable viral load at six months and failure to continue in care. In our study setting, with limited prior exposure to ART and thus limited transmitted resistance, adherence is the main and most important determinant of these poor treatment outcomes. Therefore, we remain interested in identifying modifiable behavioural exposures that impact adherence and in turn predict poor treatment outcomes through adherence.

We agree with the reviewer that among a limited number of individuals detectable virological outcome at 6 months may reflect transmitted resistance to ART. However, because the majority of patients in low income countries were started on highly efficacious triple therapy regimens and had limited access to treatment prior to the availability of triple combination therapy, the prevalence of drug resistance is likely to be less than 5% in most low-income countries [1]. HIV drug resistance threshold surveys based on WHO guidelines were conducted in 2005 and 2006 in several low-income countries. Under the survey guidelines HIV infected primagravidae women attending antenatal care and less than 25 years of age were sampled to investigate resistance. In Swaziland of the 70 specimens collected, 44 were
genotyped and the level of transmitted resistance to all relevant drug classes was classified as <5% [2]. Similarly, with comparable sample sizes in Malawi [3], Tanzania [4], and Ethiopia, the level of transmitted resistance to all relevant drug classes was classified as <5%. In a similar study conducted in South Africa in 2002 and in 2004 on 113 samples collected from pregnant women attending antenatal care, the level of transmitted resistance to all relevant drug classes was also classified as <5% [5]. We also acknowledge the use of nevirapine for the prevention of mother to child transmission may also contribute to resistance on ART. Nevirapine resistance has been shown to emerge in approximately 19%-76% of women 2-8 weeks after the administration of single dose nevirapine [6]. However, a recent review of the effect of nevirapine on resistance by McConnell et al. highlighted several studies that suggest that the efficacy of NNRTI-containing treatment regimens can be maintained among women previously exposed to single dose nevirapine [6]. The review highlighted two studies in Botswana and Thailand that suggest that efficacy is maintained so long as treatment is commenced >6 months after exposure [7-8]. Thus, in low income countries even with access to PMTCT, detectable viral load is acknowledged to be in most part due to poor adherence [9-10].

Comment 2
A more detailed explanation of the hierarchical framework is needed as many are not aware of this approach. It certainly adds to the analytical approach but it makes it a little harder to compare to other studies findings.

Response to comment 2
We have added a more detailed explanation of the hierarchical conceptual framework in a new Annex 1. The approach of using a hierarchical framework to organize the conduct of the multivariate regression, which is well described by Victora et al. [11], strengthens the analysis approach from one solely based on statistical associations to one that considers the potential relationships between exposures and the outcome of interest as well as among exposures. This allowed us to better investigate potential confounding and co-linearity between these factors in order that we don’t underestimate the effects of distal factors. The additional text in the new Annex 1 is as below:

Annex 1: Hierarchical conceptual framework for multivariable analysis
In the hierarchical conceptual framework used to conduct multivariable analysis, factors of interest were organized into three levels according to how directly they were thought to influence adherence behaviour [11]. Distal level exposures of interest were factors thought to affect adherence behaviour indirectly or through other mediating factors. These primarily included personal characteristics and experiences with healthcare services. Intermediate level exposures of interest were factors thought to mainly affect adherence through more proximate determinants. These intermediate level factors primarily included factors related to beliefs regarding HIV and traditional medicines. Finally proximate exposures of interest were ones thought to more directly influence adherence behaviour. This included factors related to beliefs in ART, disclosure and adherence to prior chronic treatment. This subdivision facilitated the organization of variables according to their theoretical hierarchical relationship to each other and to the treatment outcome. Organizing variables using these theoretical hierarchical
relationships was deemed important for two reasons. Firstly, to avoid the misclassification of proximate factors as confounders of the distal determinants and the reduction or nullification of the true effect of the more distal determinants [11]. Secondly, the hierarchical classifications enabled the grouping of similar variables into the same hierarchical level in order to facilitate the assessment of co-linearity among variables.

**Steps in the multivariable analysis**

Variables found to be associated with the outcome in the univariable analysis (P <0.20) and any potential confounders were further grouped into three hierarchical levels. Firstly distal level exposures of interest were analysed, starting with a full model that included all distal level exposures found to be associated with the outcome in the univariable analysis (P <0.20) and any potential confounders. Explanatory variables were then sequentially dropped from the model, starting with variables with the weakest association with the outcome based on the likelihood ratio test. Only variables found to be associated with the outcome at a p-value smaller than 0.10 and a priori confounders were retained. Secondly, the full intermediate level model included distal level determinants identified in the previous model, intermediate level exposures found to be associated with the outcome in the univariable analysis (P <0.20) and any a priori confounders (see Table 8-2). Finally at the proximate level, exposures of interest were analysed starting with a full model that included distal level determinants, intermediate level determinates, all proximate level exposures found to be associated with the outcome in the univariable analysis (P <0.20) and any a priori confounders.

At each level, variables thought to be highly correlated within each group were cross-tabulated in order to investigate collinearity. Two tests for collinearity, tolerance and Variance Inflation Factor (VIF), were calculated to test the strength of the interrelationships among the variables. Tolerance is an indicator of how much collinearity a regression analysis can tolerate, while VIF is an indicator of how much of the inflation of the standard error could be caused by collinearity [12]. If collinear variables were identified one variable, that with the strongest association with outcome, was chosen to represent the collinear variables in the group.

Explanatory variables were then sequentially dropped within each group starting with variables with the weakest association with the outcome based on the likelihood ratio test. Only variables found to be associated with the outcome at a p-value ≤ 0.10 were retained. This threshold was chosen (as opposed to more conventional 0.05) to minimize the chances of erroneously excluding potentially important risk factors [13-14]. However, the interpretation of the models considered not only the magnitude of the association (size of the odds ratios) but also the precision of the point estimates (width of the confidence intervals) [13]. The model presented in the paper is the final model in which the effects of proximate variables adjusted for confounding role of distal and intermediate variables.
Sensitivity analysis

Since there may be more than one logical way in which variables could be grouped, a sensitivity analysis was conducted to test the potential effect on regression analysis of employing an alternative hierarchical framework. In this alternative conceptual framework key factors identified to be associated with poor adherence in the primary regression analysis were reclassified at different levels in the hierarchy to test if and how this would change the models obtained from the primary regression analysis. For example, beliefs in HIV and traditional medicines were reclassified as distal factors, and factors related to education and income were reclassified as intermediate factors. Factors related to beliefs regarding ART and experience with chronic medications remained classified as proximate factors.

Comment 3
Study duration dates needed in the Methods. It seems the sample size calculated by the study team was never achieved and it is not clear what proportion of potentially eligible patients seen in each of the programs was included. Given the large size of these programs, it is likely that there are several patients seen each week that would be potentially eligible for this study. How representative are the 227 in the community program and the 117 in the workplace program? Over what period of time were they enrolled?

Response to comment 3
As suggested the following statement was added to the participant paragraph of the results section (see page 7 of the manuscript, paragraph 1).

*Enrolment of study participants took place between May 2006 and February 2007 and follow-up continued until September 2007.*

The sample size of 400 participants was the maximum enrolment target. However, we were aware prior to study initiation that we may not reach this target since enrolment depended upon the rate of new patients initiating ART, which was beyond the control of the study team. Accordingly, in the study protocol we calculated the odds ratios that could be detected based on potential sample sizes ranging from a maximum of 400 to a minimum of 300 participants. We have now added the following sentence to the sample size paragraph in the methods section (see page 5, paragraph 4):

*A sample size of 300 would have enabled the detection of an odds ratio of 4 for any risk factors with a prevalence of 15%-35%.*

The local ethics committee required that potentially eligible patients were first approached by clinic staff and referred by clinic staff to study staff to hear more about the study. Thus we do not know what percentage of all patients starting ART would have met study eligibility criteria. Among potential patients seen by study staff, 100% and 98% of those eligible in the community and workplace programmes, respectively, were enrolled (as shown in Figure 2). The main comparisons made in the analysis are valid as they are within the cohort. However, we can not be sure that the prevalence of specific baseline characteristics is representative of all patients starting ART in these clinics. In
accordance with your comment, we have added a description of this in the limitations section (see page 11, paragraph 2) which reads as follows:

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 baseline characteristics is representative of all patients in the clinic who were eligible for the study. Nonetheless, the study analysis compared data within the cohort and thus was valid in ascertaining which characteristics were associated with the outcomes observed. This is especially considering that the refusal rate once patients were offered study participation was very low (0% in the community and 2% in the workplace programme).

Minor revisions

Comment 4
Abstract: 2nd sentence is missing a word "This is especially important _____since..."

Response to comment 4
The abstract was completely revised in accordance with the overall comments of both reviewers (see page 2 of the manuscript).

Comment 5
Sentences usually do not begin with numbers

Response to comment 5
We agree generally, but most style guides suggest that a sentence may begin with a number if written out as a word. We will defer to the journal house style on this point.

Comment 6
In results, include adherence information from 6 week visit and compare to 6 month visit as this would provide a more dynamic description of adherence over time.

Response to comment 6
We believe the analysis suggested is valuable but that it would be better presented in a different paper focusing on comparing methods of measuring adherence.
Reviewer: Paula Braitstein

Reviewer's report:
General remarks: Adherence to antiretroviral treatment is a critical issue in the implementation and success of HIV treatment programs. The investigators are to be commended for attempting to address this complex issue in a prospective manner, and also for considering a multitude of social and cultural factors that can affect adherence but which are normally overlooked in scientific studies. The investigators chose to use cross-sectional evaluation of plasma viral load and treatment discontinuation as their measure of adherence, although neither constitutes a normally accepted definition, even by proxy, of adherence to antiretroviral treatment. Thus although they are calling their outcome ‘adherence’, it really is not adherence – it is undetectable viral load and/or treatment continuation beyond 6 months (and have excluded a swathe of patients who either died or became lost to follow-up which may have led to a whole other level of bias). In other words, it is impossible to interpret these data in terms of true adherence to treatment. “Medication adherence may be defined as the extent to which a patient takes a medication in the way intended by a health care provider.” (http://hivinsite.ucsf.edu/InSite?page=kb-03-02-09). Do the authors really agree that cross-sectional measures of plasma viral load and complete treatment discontinuation fulfill this definition?

Response to reviewer report
We thank the reviewer for highlighting the strength of the prospective design as well as the depth and variability of the factors assessed. As regards the outcome definition, kindly see response to Dr Gupta’s comment 1 on page 1 of this document.

Major Compulsory:

Comment 1
There is potentially an important selection bias since there is no information about the numbers or characteristics of people who declined to participate (referral bias, ascertainment bias). Similarly, excluding all patients who died before the 6 month visit or who became lost to follow-up may have led to additional bias, especially given that ‘treatment discontinuation’ is one of the two outcomes.

Response to comment 1
Among potential patients seen by study staff, 100% and 98% of those eligible in the community and workplace programmes, respectively, were enrolled and therefore refusal for study participation was minimal.

Regarding referral bias kindly refer to our response to comment three of Dr Gupta’s comment (page 4 of this document).

Finally, as regards exclusion of those dead before six months: Individuals known to have died before six months were excluded from the analysis, because our main interest was in factors affecting adherence,
and early mortality on ART is more likely due to advanced disease at ART start and comorbidity than poor adherence [15-16]. This was especially considering that in our cohort the majority (82%) of those who died had in fact died less than three months after treatment initiation.

Comment 2
It is very good to include a conceptual model but it hasn’t been validated and should really form its own manuscript. Thus basing the multivariable modelling upon this conceptual model seems premature. Including more detailed information about each of the variables considered and how they were measured and defined in the analysis is essential.

Response to comment 2
We used the conceptual framework as a tool in the statistical analysis, to guide the order in which variables were introduced into the logistic regression analysis, in line with the method of Victora et al [11]. This is to take into account not only statistical association at the univariate level but also to think about potential relationships to the outcome and to other similar exposures. This analysis approach was used to help examine confounding and co-linearity. It was not meant to present a validated description of how adherence works in this setting. We agree that additional information on the variables considered in the conceptual framework would be helpful and have included an annex to further describe the process (see response to comment 2 in Dr Gupta’s review).

Comment 3
I remain unconvinced by the rationale presented for defining adherence based on a detectable viral load at 6 months or discontinuing antiretrovirals after 6 months. The references cited (in the discussion) do not appear to support this definition either. There are a multitude of reasons why a person may have a detectable viral load after 6 months – sub-optimal therapy (regimens are not described), co-administration of anti-tuberculosis medications resulting in drug-drug interactions (not mentioned in the methods), poor absorption due to diarrhea and other illnesses (not mentioned), to name a few. Although plasma viral load can be used to validate adherence measures, it does not in itself constitute a reliable measure of adherence.

Response to comment 3
As suggested, we have added the description of the ART regimens used (see page 4, paragraph 1). The revision reads as follows:

This study was conducted within two ART programmes in South Africa. The first was a community programme located within a tertiary public sector hospital serving a diverse periurban population in Johannesburg. HIV treatment and care, including laboratory testing and treatment for opportunistic infections, were provided free of charge but patients were expected to cover other expenses such as transport to the clinic. The first line ART regimen was d4T/3TC/efavirenz, or nevirapine if efavirenz was contra-indicated. Most patients self-presented for treatment after undergoing voluntary counselling and testing (VCT) in a primary health centre. The second study site was a workplace programme located within a tertiary mining company hospital in the Northwest Province. The hospital provided free HIV treatment, including laboratory testing and treatment for opportunistic infections, and care to mine
employees as well as free transport to the clinic. The first line ART regimen was Combivir (AZT+3TC) and efavirenz, or nevirapine if efavirenz was contra-indicated. Most patients were referred for treatment after undergoing counselling and testing offered as part of regular VCT campaigns; yearly employment health examinations or provider initiated testing and counselling (PITC).

As described above, we have reframed the outcome from “adherence” to “treatment outcome”.

Comment 4
4. Similarly, treatment discontinuation is conceptually different from non-adherence and may be caused by toxicity, co-administration of anti-tuberculosis medication, etc. Presumably the investigators could have used self-reported adherence, pill counts, pharmacy refills, or one of the other commonly accepted measures of adherence. Furthermore, a single cross-sectional adherence assessment (as the investigators have done at the 6 month visit) is considered insufficient for measuring adherence with any degree of accuracy.

Response to comment 4
We measured self-reported adherence, but used detectable VL as a marker of poor adherence because it is not affected by social desirability bias and is a key prognostic marker for individuals on ART. It is true that a single marker of adherence - such as self report or pill count at any specified time point - may not be an accurate indicator of adherence over the longer term. However, virological suppression at 6 months after ART start among ART-naïve individuals in settings with a low prevalence of transmitted resistance is likely to be an indirect marker of cumulative adherence over that time period.

Additionally, patient-initiated treatment discontinuation could be considered the most extreme form of poor adherence. The exclusion of treatment discontinuation in poor adherence studies is an acknowledge limitation of many of these studies and is largely due to the logistical and financial constraints that prohibit active tracing of patients who discontinue clinical follow-up in order to confirm reasons for attrition. Indeed few studies have reported on treatment discontinuation subsequent to discontinuation of clinical care and this exclusion leads to underestimation of mortality [17] as well as an underestimation of poor adherence levels.

Comment 5
5. Table 2 is incredibly difficult to read or interpret and could be dropped.

Response to comment 5
Readers may find detailed information on associations with poor outcome, and the contrast between associations in the two settings, useful. So we propose to retain the table since a major advantage of on-line journals is that space is less constrained. However, we can remove it if the editors feel it is redundant.

Comment 6
There is insufficient information in the methods and in the tables to allow for accurate interpretation of the data presented. For example in Table 3, what is the reference category for the outcome? Although it
makes sense that men are less likely to be “adherent”, it doesn’t make sense that knowing someone on ART makes you less likely to be adherent. There is nothing in the methods or the table to tell us how the outcome was coded.

Response to comment 6
As suggested we have clarified how the outcome was coded in Tables 2 and 3 in the manuscript (see page 18 and table 3 file). The revised headings for the tables now read as follows:

**Table 2: Univariable level predictors of poor treatment outcomes (viral load >400 copies/ml and complete discontinuation of follow-up and treatment six months post treatment initiation) on antiretroviral therapy in community and workplace programmes**

**Table 1: Baseline predictors of poor treatment outcomes (viral load >400 copies/ml and complete discontinuation of follow-up and treatment six months post treatment initiation) on antiretroviral therapy: univariable and multivariable adjusted models**

We agree that “it doesn’t make sense that knowing someone on ART makes you less likely to be adherent”. However, our findings show that knowing someone on ART was associated with BETTER adherence (see tables 2 and 3 in the manuscript) and so are in line with what we would intuitively expect.

**Comment 7**
The concerns about how the outcome is defined affect the entire interpretation and discussion. For example, the finding that individuals who were started on cART within 2 weeks of a diagnosis were ‘poor adherers’ doesn’t make intuitive sense – these people are obviously very sick, and previous studies show a strong relationship between advanced disease and good adherence. More likely is that these people are very sick – in other words had a very high baseline plasma viral load, and it can take more than 6 months to have an undetectable viral load.

**Response to comment 7**
In the workplace programme (where earlier ART initiation was associated with poor adherence) starting ART within 2 weeks of testing for HIV was not associated with lower CD4 counts or higher viral load at baseline compared with people who started ART more than two weeks after testing for HIV. As described in the paper, intensified HIV screening and rapid ART initiation largely reflected the strong commitment to improving access to ART to individuals in need of treatment, as soon as they were confirmed to be eligible for treatment. We hypothesized that this approach extended ART to a “second generation” 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. This relatively unusual setting of facilitated access to ART may have inadvertently resulted in individuals starting ART who were less motivated to adhere to, and succeed on, treatment.

**Comment 8**
The authors are incorrect that there is no Gold Standard for measuring adherence: both MEMS caps and plasma drug levels are considered Gold Standards.
Response to comment 8
Plasma drug monitoring, electronic monitoring and direct observation of therapy (DOT) assessment are regarded as more objective proxy measures of adherence in comparison to self-reported adherence. However, the each of the above mentioned measures have their widely acknowledged limitations that preclude their being a “gold standard” for measuring true adherence [18-19]. Adequate plasma drug concentrations have been shown to correlate with virologic suppression. However, plasma drug concentration levels only reflect recent drug consumption and thus may not detect earlier non-adherence to treatment [19]. Additionally, plasma drug concentration levels may be affected by factors other than adherence, such as drug interactions and diet [19]. Electronic monitoring devices work by monitoring the opening of the ART pill bottle using an electronic-chip-fitted cap. This enables the measurement of levels and patterns of pill consumption. However, electronic monitoring may not measure actual pill taking and may underestimate adherence if multiple doses are extracted at one time [18-19]. Another objective method of measuring adherence is DOT. However, this method may not fully guarantee that the patient actually took the drugs and was therefore adherent [20].

Minor Essential comments:

Comment 9
9. Introduction - Update WHO statistics on rollout. Data presented are outdated.

Response to comment 9
As suggested, the introduction was updated using 2008 data (see page 3, paragraph 1 in the manuscript). The revision now reads as follows:

Yet by 2008 only 42% of those in need of antiretroviral therapy (ART) worldwide were receiving treatment [21].

Comment 10
10. ART is provided free but what about labs? Treatments for opportunistic infections and/or side effect management? Other diagnostic tests? These issues might not directly affect adherence, but they could certainly affect viral load and the likelihood of treatment discontinuation (for example, through unmanaged toxicity).

Response to comment 10
HIV care and treatment including management of opportunistic infections and side effects as well laboratory exams are all provided free of charge. As suggested, this has been clarified in the methods section (page 3, last paragraph). The revision reads as below:

This study was conducted within two ART programmes in South Africa. The first was a community programme located within a tertiary public sector hospital serving a diverse periurban population in Johannesburg. HIV treatment and care, including laboratory testing and treatment for opportunistic infections, were provided free of charge but patients were expected to cover other expenses such as transport to the clinic. The first line ART regimen was d4T/3TC/efavirenz, or nevirapine if efavirenz was contra-indicated. Most patients self-
presented for treatment after undergoing voluntary counselling and testing (VCT) in a primary health centre. The second study site was a workplace programme located within a tertiary mining company hospital in the Northwest Province. The hospital provided free HIV treatment, including laboratory testing and treatment for opportunistic infections, and care to mine employees as well as free transport to the clinic. The first line ART regimen was Combivir (AZT+3TC) and efavirenz, or nevirapine if efavirenz was contra-indicated. Most patients were referred for treatment after undergoing counselling and testing offered as part of regular VCT campaigns; yearly employment health examinations or provider initiated testing and counselling (PITC).

Discretionary comments

Comment 11
Abstract – Introduction very long

Response to comment 11
The abstract introduction was shortened.
References


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


