Reviewer's report

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

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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?

Major Compulsory:

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.

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 modeling 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.

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.

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.

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

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.

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.

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.

Minor Essential:
1. Introduction - Update WHO statistics on rollout. Data presented are outdated.  
2. 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).
Discretionary:
1. Abstract – Introduction very long

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.