Reviewer's report

Title: Adherence to antiretroviral therapy among HIV infected children measured by drug level, medication return and caretaker report in Dar es Salaam, Tanzania

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Reviewer: Christos Karatzios

Reviewer's report:

This manuscript describes a cross-sectional study performed at Muhimbili University of Health and Sciences in Tanzania and aims to answer the question of whether adherence to antiretroviral medication(s) is best reflected by patient or caretaker self report, medication return/counting, or therapeutic drug level monitoring. The conclusion was that therapeutic drug level monitoring does not agree with self report or medication return and the authors hint that therapeutic drug level monitoring is a more reliable way to test adherence in the subject groups studied and in general. This is an interesting question that has been answered previously (but not in Tanzania) and we often do use therapeutic drug level monitoring to indirectly assess adherence to antiretroviral therapy especially in pediatrics.

Apart from this, my comments can be seen below.

MAJOR COMPULSORY REVISIONS:

1) The question that the authors pose is well defined, the methods were appropriate, and the data (including the statistical analysis) is sound. However this cross-sectional study could have taken the question to a higher and more interesting level for me. While the authors can truthfully state that as per the methods they used, they are able to conclude that proportionally therapeutic drug level monitoring of the drug nevirapine reflected worse adherence when compared to self report or medication return, I do not think they can infer, with the data presented as is, that “Nevirapine plasma concentration measurements should be used to assess adherence to nevirapine based antiretroviral regimen [sic] in HIV infected children.” As I mention just above, specifically I would have liked to see a breakdown of two groups of patients (those with undetectable viral loads and those with detectable virus in their blood) and the respective agreement of their self report/medication return versus their drug level monitoring. This would have shown us whether the ones with a higher disagreement had worse clinical/virologic outcomes. Consequently, we are not given this information in the paper and we are only told who was immune suppressed. Perhaps viral load measurements are not easily available to the investigators?

2) There are limitations to this study that are not adequately (or not at all) discussed in the manuscript. This is a cross-sectional study in which one blood
sample per patient was analyzed for nevirapine concentration. A single sample is inadequate to make the general inference that someone is non-adherent to their medications – especially if we are not told what their virologic control is. Fluctuations in bioavailability, time of day of administration of the drug and drug level sampling may affect the result and bias it to “non-adherence” if the level was low. The authors do not mention that if an otherwise adherent patient (as defined > 95% adherent, and/or with an undetectable viral load) did not or could not take his/her nevirapine for whatever reason in the 1-2 days before sampling, the level could be low. This would overestimate the non-adherence. The study would have been “richer” if many samples were taken over a period of time.

While the authors allude to this briefly, another limitation (opposite to the one described above) is a potential for underestimation of the non-agreement between self report/pill counting and serum drug levels: Nevirapine has a long half life (almost 48 hours) and in some individuals, the level is adequate and therapeutic for a longer time than others especially if they are slow metabolizers. Therefore, it is possible that in certain non-adherent patients (that may have reported they took their dose 4-6 hours before blood sampling was done), a therapeutic level may have been falsely normal if they didn’t take their medications regularly but had slow nevirapine metabolism and prolonged high levels.

A third limitation that wasn’t discussed is that some otherwise non-adherent patients could have taken their nevirapine the few hours before in anticipation of a blood test, and they would have had a normal or therapeutic drug level. This would of course underestimate the non-agreement between self report/pill counting and serum drug levels.

These are important limitations that should have been addressed and/or discussed by the authors.

MINOR ESSENTIAL REVISIONS:

There are many spelling, grammar, and syntax mistakes throughout the document. I fully understand that the authors’ mother tongue may not be English and I would suggest they use the help of a language editor to proof-read and rewrite the manuscript. In general, the manuscript’s writing and message are understandable but there is a mistake on practically every second line especially in the Methods and Results sections. This makes for difficult reading and does not reflect professionally.

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

Quality of written English: Not suitable for publication unless extensively edited

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.