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

Version: 1 Date: 24 March 2013

Reviewer: Jason Brophy

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REVIEWER’S REPORT

Major Compulsory Revisions:

1. The main flaw of this paper is that it fails to convincingly make the case that inadequate nevirapine concentrations are solely due to poor adherence. There are several issues the authors do not address that contribute to this failure.

First is the issue of pediatric drug dosing. Previous publications have stressed the importance of adequate dosing of nevirapine in young children, with a dose of 300 mg/m2/day recognized as essential to achieve adequate drug concentration for virologic suppression. I would prefer to see median nevirapine dose reported for the entire population as well as median dose for the groups with adequate (>/= 3 ug/mL) versus inadequate (<3 ug/mL) nevirapine concentrations. If drug dose was adequate and the same in each subgroup, that would strengthen the argument for non-adherence.

In addition to or in lieu of drug dose, reporting of drug formulation would be very important for the authors to consider. Previous literature has demonstrated that children treated with split tablets of adult three-drug combination formulations (ie. stavudine-lamivudine-nevirapine) are often underdosed for the nevirapine component of the combination. This relates to the variation in weight versus body surface area in children (particularly at younger ages), as well as the differences in clearance of nevirapine by younger children (particularly those < 8 years of age). Pediatric fixed dose combination tablets (of stavudine-lamivudine-nevirapine or zidovudine-lamivudine-nevirapine) are specifically formulated for children to ensure adequate nevirapine exposure. Hence, even if the nevirapine dose (mg/m2/day) could not be calculated, clarification that the appropriate use of pediatric fixed dose combinations took place for the patient population in this paper would assure the reader that the children were receiving the proper dose of nevirapine. This would strengthen the argument that low nevirapine concentrations were due to non-adherence and not under-dosing.

Along the same lines, the authors do not make mention of the issue of tuberculosis treatment. It is well known that the drug interaction between rifampicin and nevirapine (with induction of the CYP2B6 and CYP3A4 enzyme
systems by rifampicin) can lead to dramatic reductions in nevirapine exposure. Hence, any children who are receiving simultaneous treatment with rifampicin for tuberculosis would be at risk for inadequate nevirapine concentrations even with appropriate drug dosing and good adherence. The authors need to mention whether any patients in this study were receiving co-treatment for tuberculosis; ideally, these patients would be excluded from the analysis, or described as a separate group.

I refer the authors to the following publications for assistance in improving these aspects of their submission:


2. The authors mention a sample size of 200 was calculated, but do not detail how this calculation was performed. More detail is needed.

3. Timing of sample collection for therapeutic drug monitoring is an important factor contributing to the reliability of results. The authors mention that all samples were collected 4-6 hours post-dose. This seems like a very narrow window for sample collection for such a large group and would normally be quite difficult to achieve outside of clinical trial conditions. More description of how such well-timed blood collections were achieved would help convince the reader.

4. There are many grammatical, spelling, and punctuation errors throughout the submitted manuscript. Many of these relate to errors with pluralization of words or missing articles (of, the). The manuscript needs major revision for quality of writing before it could be considered for publication.

**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.