Reviewer’s report

Title: Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study.

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Reviewer: Lauren Wood

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Review BMC Pediatrics Manuscript

Title: Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study.

Authors: Davies MA, Boulle A, Fakir TR, Nuttall J and Eley B.

Reviewer: Lauren V. Wood, M.D.

Date of Review: 03/27/08

Declaration of Competing Interests: I have no financial or non-financial competing interests in relation to this paper.

General Comments for the Authors:

This is an extremely well written article that dresses a difficult but critically important aspect of antiretroviral treatment: adherence to therapy in the treatment of HIV-infected children. The issue of adherence and assessing it is challenging in and of itself; addressing the issue in HIV-infected children adds another level of complexity in that adherence involves a parent or caregiver, as does antiretroviral treatment in resource poor settings. The authors have done an outstanding job in attempting to identify a methodologically acceptable surrogate of adherence that correlates with clinical outcomes in this setting.

Recommendation: Accept for publication

Minor Compulsory Revisions: NONE

Minor Essential Revisions:

1) In the abstract Results section add the following for clarification: “Questionnaires were completed by 87/98 (90%) of caregivers of children remaining in care after 3 months. Sensitivity of poor self-reported adherence (missing > 1 dose in the previous 3 days) for MR adherence <90% was only 31.8% (95% CI: 10.7-53.0%).”

2) In Figure 1, please clarify how the authors reached a Median (IQR) occasions of MR of 12 for the 115 children who returned medication on at least one occasion. Since the study was only 1 year long, there were only 12 possible
months at which medication could be returned. A median value MR return of 12 suggests that all 115 patients in the study returned their medications on every occasion. This clearly isn’t the case since in their calculation of annual average MR adherence they assigned a value of <90% adherence for missing returns in children not returning medication on all possible occasions. It would seem to me that the mean and the median for this value would have to be something less than 12 given that 100% of the study participants did not return their medications at 100% of the possible study timepoints.

3) On Figure 2, X axis label clarification: “Adherence Assessment by Medication Return (MR)”

4) On Figure 3, Y axis label clarification: Percent of Children with Adherence <90% by MR”

Discretionary Revisions: Addressing these would strengthen the paper and address the few minor weaknesses that the publication has.

1) Would consider including in the abstract results that medication return (MR) did not correlate with CD4 outcomes. The authors do mention this in the results section, but since CD4 and viral load are the two most important surrogates for HIV clinical status, to mention viral load and leave out the lack of correlation with CD4 count gives an incomplete picture. It was the first question this reviewer had after reading the abstract i.e. was there any correlation of MR with CD4? Importantly, the lack of MR adherence correlation with CD4 is consistent with other methodologies used to assess adherence.

2) Would consider adding to the abstract results that adherence > 90% by MR correlated with mean weight-for-height z-score. The p-value reported in Table 1 was highly statistically significant (p = 0.02), and in resource poor settings where the number of CD4 and viral load determinations may be limited, weight-for-height z-score is a well established correlate of response to antiretroviral treatment and clinical outcomes, especially in children. To me, this is one of the most significant findings of the paper and one that should be highlighted more by the authors.

3) The paper would be strengthened by a Figure (similar to Figures 2 and 3) that documented the % of children returning medications at each study month time point during the 1 year course of the study. The authors report that medication was returned on at least one occasion for 115 of the 122 children (94%) who commenced ART. After 1 year, 88 children were alive and remained on therapy. The reviewer is interested in knowing whether or not MR changed over time during the course of the 1 year study and what was the exact breakout of the 115 children who had medication returned on at least one occasion. This is important to include given the way annual average MR adherence is calculated. Another way of addressing the issue is to get at the percentages of the 115 children who had MR at 12/12 months, 11/12 months, 10/12 months, 9/12 months etc and determine whether or not there is a cut-off in # if MR months that correlates with worse clinical outcomes. Also see comment 2) under Minor Essential Revisions.

4) Were there any differences documented in MR for children on regimens
containing syrups/solutions vs. those on tablets/capsules regimens exclusively. Given the documented challenges in administering solutions (often unpalatable) to children, it’d be interesting to know if there was a difference MR adherence between the two groups.

5) Did the authors examine whether dosing changes in the antiretroviral regimen impacted MR adherence i.e. were the children who <90% adherent more likely to have undergone a dosing change during the 1 year course of the study?

6) The authors readily acknowledge two of the major weaknesses of the study:
- That measurement of self-reported adherence by interview questionnaire being administered by clinicians may have caused caregivers to report higher adherence to please the interviewer and hence, why self-reported adherence correlated poorly with MR adherence and viral load.
- That the percentage of children with > 90% MR adherence may have been so high because of the nature of the patient population selected for study as these “were among the first children to receive ART and were well known to the HIV service as adherent with other medications and clinic visits.” (p.14) What the authors do not acknowledge as potentially having introduced further bias into the study population is the original selection criteria for commencement of ART. In addition to the recommendations of the 2001 European treatment guidelines in “selective social criteria that assessed treatment readiness and caregiver willingness to comply with regular monitoring” were utilized to determine which children would begin therapy. (p.5) Since these criteria could clearly enrich for patients more likely to be adherent, the authors should elaborate further what were the selective social criteria.

7) Did the authors tease out statistically if socio-economic status was just a surrogate marker for better education or vice versa? While both were independently associated with better adherence is it because they are just different markers for the same thing i.e. the ability to have better housing, access to water and electricity etc.

8) How do the authorize reconcile their observations that taking ritonavir was negatively associated with MR > 90% adherence (last line of abstract results p.3) but patients taking ritonavir were more likely to have excess MR adherence than those on efavirenz using the uncapped annual average MR adherence calculation? Why do the authors think the uncapped MR adherence was higher with the ritonavir group when overall because of poor palatability etc. ritonavir generally posed a barrier to adherence?

Level of interest: An article of importance in its field

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.