Author's response to reviews

Title: Renal abnormalities among HIV-infected, antiretroviral naive children, Harare, Zimbabwe: a cross-sectional study

Authors:

Vongai Dondo Dr (vdondo@yahoo.com)
Hilda A Mujuru Dr (hmujuru@mweb.co.zw)
Kusum J Nathoo Prof (knathoo@mweb.co.zw)
Maxwell Chirehwa Mr (mchirehwa@yahoo.com)
Zivanai Mufandaueda Mr (zivanaimf@yahoo.co.uk)

Version: 3 Date: 21 February 2013

Author's response to reviews: see over
Reviewer's report
Title: Renal abnormalities among HIV-infected, antiretroviral naive children, Harare, Zimbabwe: a cross-sectional study
Version: 2 Date: 1 August 2012
Reviewer: Russell Pierre
Reviewer's report:

Major Compulsory Revisions
None

Minor Essential Revisions
1. Figure 1 is unclear; one cannot interpret the meaning of the blue/red bars; additionally how are WAZ, HAZ, and WHZ represented in the figure?

The blue bars as indicated on the key represent weight-for-age z-score (WAZ), height-for-age z-score (HAZ), weight-for-height z-score (WHZ) MUAC-for age >-2 and the red bars represent z-scores < -2

2. Discussion:
Is routine urine testing conducted on HIV-infected children at the authors’ institution? If not then the probable difference in age of presentation in the Chaparro study compared to current study could also be explained on the basis of routine urinary screening resulting in earlier detection

There is no routine urine testing conducted on HIV-infected children at our hospital. The point has now been included in the discussion and as a recommendation

3. Minor editorial/grammatical errors
Page 12.......Duncan set (should be….et) al
Done
Page 14......Staphylococcal aureus (preferably Staphylococcus….)
Done
Page 14 – 15….1st paragraph: the sentence needs restructuring
The majority of the E coli isolates were sensitive to ciprofloxacin 17/21(80.9%) while 61% and 52.3% were sensitive to gentamicin and nalidixic acid respectively.
Page 15, para 2……..This may suggests widespread (preferably suggest)
Done
Conclusion…….2nd sentence needs restructuring

The renal impairment is more likely to occur in children with advanced WHO clinical stages (3 and 4) and estimation of GFR should be done as part of overall assessment in HIV-infected children.

4. Table 3: this is clumsy and crowded, and actually three tables in one; authors should decide on creating one table and present the other data in the body of the text.

Tables have been separated in the manuscript.

5. Authors must clarify urine sampling methods; this has implications for the interpretation and diagnosis of UTIs based on growth pattern on microbiological media.

A midstream urine sample was collected for dipstick analysis, microscopy, culture and sensitivity.

5. Authors must review entire manuscript to address minor editorial/grammatical issues.

Done

Discretionary Revisions

Conclusions:
Authors should consider that routine urinary screening of HIV-infected children be part of the follow-up protocol (at least yearly), given that early detection of HIVAN and commencement of appropriate antiretroviral therapy may ameliorate further deterioration of renal function.

Routine urine dipstick urinalysis should be offered to all HIV-infected children since it is cheap, readily available and allows earlier detection of renal impairment. Appropriate monitoring and ART for eligible children should be offered without delay.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being Published.

The article has been read by a fluent English speaking colleague for grammatical errors.

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

Reviewer's report
Title: Renal abnormalities among HIV-infected, antiretroviral naive children, Harare, Zimbabwe: a cross-sectional study
Version: 2 Date: 10 January 2013
Reviewer: Nicola Cotugno

Reviewer's report:

1) Although the question posed by the Authors to define the prevalence of proteinuria, urinary tract infection and low eGFR is well defined, considering what reported in the text the Authors should better state that another aim of the study is to relate these events with clinical data (relating factors) which could in turn give some relevant information to physicians working in those specific setting. This should be better clarified in the introduction section.

This study aimed to document the prevalence of renal impairment, urine abnormalities and the associated factors in HIV-infected, antiretroviral naive children in a resource limited setting.

2) In the introduction, first paragraph, the first sentence seems to be quite isolated and is not well supported by the literature, Authors should clarify better the reason why “kidney disease is becoming” a public health disease, specifying in which scenario. The sentence seem to refer to general population, in this case how does it relate to HIV infected persons, and specifically, how does it relate to renal function in HIV infected children in Africa.

Noted, reference changed and now reads “Almost 30 million HIV-infected people live in Africa and sub-Saharan Africa is the single most affected region. Sub-Saharan Africa has 10% of the world’s population, yet about 60% of the world’s HIV-infected people live in the region”

3) Introduction, third paragraph. It should be stated what is changed in kidney disease after HAART era, even if the study is related to HAART naïve children. There are several studies relating HAART to renal impairment, tubular disfunction and other DAIDS event, all this part cannot be omitted even if the study is on HAART naive children.

The section has been included and other studies cited e.g. Iduoriykemwen 2013

4) Introduction, third paragraph. There is no mention of the virus related renal damage or to the damage related to the immune impairment which incur during chronic or acute phase of the infection. This issue should be discussed and supported by specific literature.

Various mechanisms of glomerular injury in HIV infection have been described [13]. The human immunodeficiency virus itself may cause kidney damage. Viral genes
env, tat, nef and vpr have been linked to the pathogenesis of renal disease [23]. Focal segmental glomerulosclerosis with microcystic tubular dilatation and mesangial hyperplasia have been documented with almost equal frequency in children. Renal parenchymal cells can serve as a reservoir of HIV and the presence of the virus can persist in the tubular and glomerular epithelial cells despite antiretroviral therapy. Entry into epithelial cells is via CD4 and CXCR4 receptors. However, HIV DNA has been found in the glomeruli of HIV-infected patients without HIVAN suggesting that other factors come into play e.g. genetics [15]. Other mechanisms include damage from circulating immune complexes, direct cytopathogenic effect on glomerular cells with undefined mechanisms, haemodynamic disturbances and nephrotoxicity of drugs used in the treatment of HIV and related illnesses [16].

5) Introduction, first paragraph, last sentence. In this case the Authors should update the literature, several papers have been published in the last 2 years and should be cited (e.g. Ekulu PM et al 2012; Ray PE 2011 etc).


6) Methods/Results. The Authors should better state why they decided to use Counahan-Barratt formula since most of the study assessing renal function in children use Schwartz formula. Authors should justify their decision otherwise a change into Schwartz formula is strongly recommended.

The Counahan-Barratt method was used rather than the Schwartz because serum creatinine was measured using the modified Jaffé reaction. When serum creatinine is estimated by the modified Jaffé reaction rather than by the enzymatic method, noncreatinine chromogens generate sufficient colour to account for about 30 µmol/dL of creatinine. The Schwartz formula tends to overestimate GFR in this case. The Counahan-Barratt formula adjusts for the noncreatinine chromogens and gives a more true value of creatinine and a more accurate GFR estimate [31-32].

7) In the Results, "WHO HIV staging of the children" paragraph. These data can be easily added to Table 1 that should clarify all the factors exposed in the entire population and in the patients presenting with persistent proteinuria.

It is a bit difficult to combine the two and deliver the message unless a separate table

8) Results, "WHO HIV staging of the children" paragraph, the Authors should state the CD4 (%; #) levels according to the different immunological stages defined by the WHO.

Added appendix I, WHO classification of HIV-associated immunodeficiency

9) Results should include the level of HIV-RNA, which are not mentioned in the manuscript. These data would be extremely important to define the phase of the
disease and in turn to define the virus-related renal impairment.

Viral load could not be done due to financial constraints and this has been added as a study limitation.

10) Discussion. Discussion should be revised and updated with more recent published findings.

Ekulu 2012, Ray PE 2011, Esezobor 2010. The other recent literature found was on adults.

11) Discussion, first paragraph. The study doesn’t show a “reduction” of the eGFR since it has not been showed in two different timepoints. Sentence must be reformulated.

This study shows a high prevalence of renal and urine abnormalities among HIV-infected ART-naïve children attending the paediatric HIV clinic at Harare Children’s hospital, with a low eGFR in 34% and UTIs in 10.9%.

12) Discussion, fourth paragraph: in this part although is clearly mentioned that young age is more likely to be associated to normal eGFR, however this is not discussed enough. Authors should discuss if it is due to the phase of the disease. Moreover as previously suggested for the introduction, the Authors should better state in the discussion the immunological and virological impact on the renal impairment.

Done.

13) Discussion "UTI" paragraph, third paragraph. Authors should state what this paragraph add to the study since it has been already presented in the table and in many other studies.

Some paragraphs removed.

14) The Authors should include more specific data on tubular damage such serum potassium and phosphorus. Moreover more specific urinary markers such as B 2 microglobulinuria, urine electrolites should be included in the analysis. If not available these limits should be better stated in the last paragraph of the discussion.

Microalbuminuria was not assessed and it has been shown to be the first marker of renal disease. Other urinary markers for tubular dysfunction such as phosphorus were beyond the limit of this study. Viral load was not done due to financial constraints but it could have helped to relate the renal abnormalities to viral load.

Minor Essential Revisions
1) Table legends should include the type of statistical analysis used. It should be stated p values what is referring to.

Done, the p values referred to was stated on section “Data analysis”

2) Levels of Blood pressure defined as “normal” should be stated and defined as an age related scale in the methods.

   Blood pressure was considered normal if it was less than 95th centile for age, sex and height

3) Figure 1 is not clear. It is not defined in the figure legend what colours in the bar plot are referring to and the 4 couples of barplots are referring to as well.
   The blue bars as indicated on the key represent weight-for-age z-score (WAZ), height-for-age z-score (HAZ), weight-for-height z-score (WHZ) MUAC-for age >-2 and the red bars represent z-scores < -2

4) In the tables, first line format (bold, curstive etc.) is not always repeated in the other lines.

   The bold was done for sub titles and statistically significant values

5) Minor revisions must be reanalyzed after the Authors provide modifications to the Major compulsory revisions.

   **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

   Edited by a native English speaking colleague

   **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.