Author's response to reviews

Title: Susceptibility to intestinal infection and diarrhoea in Zambian adults in relation to HIV status and CD4 count

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Author's response to reviews:

Thank you for the thoughtful comments of the reviewers which we have addressed below. We have made point by point changes to the paper which are highlighted in yellow in the manuscript.

Reviewer 1

The reviewer asks why we make reference to interesting findings in the literature in the introduction and discussion but “no data are shown”. The reviewer did not specify what exactly he is referring to here, but we surmise that it might be to do with enteropathy and HIV disease progression. This is of interest because we and other groups have substantial evidence (refs 5 and 18) that intestinal damage (enteropathy) is seen late in HIV disease, and is related to opportunistic infections. In the present paper we examined the relationship between HIV stage and infection and found that susceptibility to pathogens was only increased when the CD4 count had fallen below 200 cells/ul. This fits nicely with our previous work, but our data do not support the recent hypothesis put forward by Douek’s group (refs 13 and 17) that enteropathy drives HIV disease progression even early in the course of HIV infection. We have rearranged this part of the Background (highlighted in yellow) to make this justification clearer.

Specific points:

1 The reviewer is quite right to point out that there was no table of demographics, and we have now included one (new Table 1). However, both the title and the Methods section of the original manuscript clearly specified that the study participants were all adults, including a definition of adult as 18 years of age or more (highlighted in pink).

2 We have broken down Table 2 (now Table 3) to show the incidence of
infections in the HIV positive participants by CD4 count groups.

3 We have added a clarification on the definition of diarrhoea in the Methods section (pages 5 and 6). However, our original manuscript did deal with the definition of diarrhoea quite explicitly.

4 We do not understand this point. The incidence (not prevalence) of diarrhoea was clearly higher as set out in the original manuscript (from Results, paragraph 3: “In HIV seronegatives the rate was 0.068 per month and in HIV seropositives the rate was 0.153 per month” – highlighted in pink). This is exactly what one would predict and this is what we found.

5 Serum retinol was measured as one marker of nutritional status. We have included a comment to this effect (p5).

6 The hygiene scores given by the nurses are shown in the new Table 1.

7 Co-infections were found in 12 samples. This does not include non-pathogenic organisms. We have included this in the Results (p7).

8 We used the phrase “at one time or another” as not all participants agreed to HIV testing when offered. Some participants declined a test initially but decided to have a test later, and there were 6 new infections despite counselling, especially to discordant couples. We concede that this was not well expressed and have changed it to “HIV positive when tested”. We have re-phrased this whole paragraph in the interests of clarity (p7).

9 The reviewer asks “Certain non-pathogenic protozoa were less common in HIV1-infected adults: which ones and why?” The non-pathogenic protozoa which were less common were set out in full in Table 2, which is now Table 3. This table was cited in the text in the original manuscript (p8, highlighted in pink).

10 The new results of our study are set out in the first two paragraphs of the Discussion (p9-10), and in the interests of clarity we have added two extra sentences at the beginning of the Discussion (p9) to emphasise the novel findings.

11 repeat of point 7

12 We acknowledge that this was confusing. We have clarified the number of people tests in the text and in Table 1, and re-worded our findings about low CD4 counts (p7).

13 Yes, cryptosporidiosis is commoner than in European or North American series, and Isospora belli infection much commoner. We have added a paragraph to the Discussion to comment on this, and a new reference to a substantial, if old, paper on typical findings in Africa (ref 34).

Reviewer 2

1 The paper does indeed rely on microscopy for diagnosis. A small team of 4
parasitologists did this work and this lab consistently scores extremely highly in QA exercises from the National Health Laboratory Service in South Africa. We would dispute the contention that antigen analysis is superior to microscopy for detection of these parasites, even before taking into account that in a study of this scale it would have been extremely costly. In our own unpublished analysis of Triage kits for detection of C. parvum/hominis antigens, we found it to be less sensitive than microscopy. We have included more details about the media used (p5). We have clarified the number of mixed infections (with pathogens) detected under point 7 above.

2 On reflection the reviewer is right to suggest that we tone down the language used and we have done this (pp 7 and 8).

3 This is not the first time that we have reported the high frequency of detection of Citrobacter rodentium. We reported it first in 2004 in Am J Trop Med Hyg (ref 5). We have commented in the Discussion.