Author's response to reviews

Title: Cerebrospinal Fluid HIV Infection and Pleocytosis: Relation to Systemic Infection and Antiretroviral Treatment

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The Editors,
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Dear Editors,

Thank you for your review of our manuscript entitled "Cerebrospinal Fluid HIV Infection and Pleocytosis: Relation to Systemic Infection and Antiretroviral Treatment." We appreciate the insightful comments in the reviewer's critique, and are pleased that this reviewer considers the paper "of importance in its field." We agree with the reviewer's ideas for 'Minor Essential Revisions,' and feel that the manuscript is improved in clarity now that these changes have been made. What follows is a point-by-point response to the reviewer's comments (quoted at the start of each point), with indications of how, and at what point in the manuscript, we have addressed each of the reviewer's points. Overall, beside the points below, the paper has been shortened by two pages, and a new author has been added to the paper.

1) ...Present the clinical cases in a table, which would shorten the paper considerably.
The nine clinical cases previously reported in pages 9-12 of the manuscript have been summarized in tables. The first five cases, illustrating aspects of genotypic and phenotypic drug resistance and clinical responses to therapy, have been documented by adding further clinical, therapeutic, and historical detail to Table 2, which had previously only contained genotypic and lab data from these individuals. The following four cases, documenting the neurological responses to antiretroviral therapy in subjects with active AIDS Dementia Complex at baseline, are now presented in a table below the correlating graphs in Figure 6, with each subject's clinical background, medication regimen (see below), and clinical follow-up shown. Brief discussions of the main relevant findings of this data remain in the text, with reference to the related data presented in Table 2 and Figure 6.

2) ...They should improve the table on clinical data of the study subjects, i.e. provide information on the CDC stages and duration of HIV-1 positivity of the study subjects.
We have expanded Table 1, "Baseline Characteristics of Study Subjects," to include the requested data for all subjects for whom this information is available (see new columns, "CDC Stage C3" and "Duration of Infection," in Table 1). The number of subjects for whom this data is available (duration of HIV infection, in particular, is not known with accuracy in many of our subjects) is indicated in footnotes to Table 1. We agree that this is relevant information which helps the reader understand the population represented in our study.

3) ...also, more precise information on duration and history of HAART in the individuals is warranted... HAART history would make clear whether there are individuals with more or less drugs said to be able to penetrate into CSF.
As noted above, we now present the detailed medication history of each individual presented in the nine cases, including baseline therapeutic regimen (or absence of therapy), the regimen initiated at study entry, and each regimen change. This precise documentation of HAART regimens is presented in Table 1 and Figure 6 in conjunction with serial CD4 counts, viral loads, and other clinical parameters, to allow the reader
a better sense of what impact these changes may have on each individual subject's clinical course. Although a comprehensive discussion of the complex topic of cerebrospinal fluid (CSF) penetration of antiretroviral medications is beyond the focus and scope of this paper, we agree that the question of whether CSF penetration of antiretroviral medications impacts upon treatment of central nervous system HIV infection remains a topic of importance and interest. As a result, we have incorporated this data into Table 1 and Figure 6 for reference, indicating those medications thought to penetrate into the CSF in green font versus black font for non-penetrating medications. Furthermore, we have added to the discussion of this issue on page 12 of the modified manuscript. We now include our analysis indicating no significant difference between the mean number of CSF penetrating medications in the antiretroviral regimens of subjects in the failed and successful treatment groups (see page 12, 1st paragraph). A more extensive presentation of data regarding CSF penetration of HAART in a separate study cohort and a detailed discussion of this topic will be presented in a forthcoming manuscript.

We hope that the editors will agree that we have revised the manuscript according to the thoughtful comments raised by the peer reviewer. Thank you very much for your consideration for publication in BMC Infectious Diseases. Please contact me with any further questions.

Sincerely,

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