Author's response to reviews

Title: Clinical outcomes and immune benefits of anti-epileptic drug therapy in HIV/AIDS

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Author's response to reviews:

April 9, 2010

Dr. Sabina Alam
Senior Scientific Editor
BMC Neurology

Dear Dr. Alam:

RE: M/S# 1675548424334557/Clinical outcomes and immune benefits of anti-epileptic drug therapy in HIV/AIDS

Thank you for your email of April 6, 2010 indicating the above manuscript had been reviewed by three referees, and had met with very positive comments. We have addressed the concerns raised by Referees 1 and 3 in a point-by-point manner in attached pages. We have also included sections defining competing interests and authors' contributions as requested by the Editor. The manuscript has been revised in response to each of the Referees’ requests and comments. We hope that the manuscript is now acceptable for publication in BMC Neurology.

Thank you for your continued interest in our manuscript.

Sincerely,

Christopher Power
Professor
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Referee 1

I feel there should be some explanation if available as to why CD4 counts were higher in the viraemic vs aviraemic patients. The clinical aspect of the study is well controlled although it is not fair to have twice as many aviraemic vs viraemic patients. Is this corrected for with the statistics as assumptions and interpretations could be incorrect or would have to be re-validated?

• We thank Referee for his comments, but would like to clarify that the higher CD4+ T cell count in viremic patients showed in Table 1 as median baseline CD4+ T cell represented CD4+ T cell levels at the time of HIV diagnosis as described in page 10 under the topic of Demographic and clinical features of AED-exposed persons. In fact, there was no difference in the mean CD4+ T cell levels at the onset of calcium channel blocking AEDs and valproate initiation in aviremic and viremic patients (0 month in Figure 4C and 4D). The mean CD4+ T cell levels at month 0 of sodium channel blocking AEDs in viremic patients was significantly lower than aviremic patients.

• We agree with the Referee that it might bias the findings to have higher numbers of patients in the viremic group compared to the aviremic group. As a longitudinal retrospective analysis, we had no control of the number of patients in each group. Nonetheless, our statistical analyses (parametric and non-parametric) account for group size differences.

It appears from the discussion that they are building on the results obtained especially with the sodium and calcium channel effect on CD4 counts which is indeed intriguing and clearly requires further investigation in for instance cART naive patients.

• We appreciate the Referee positive comments and hope to pursue these questions in the future study.

Referee 3

1. Clinical outcome as the title suggest was not really studied. The study is in vitro but the title suggests a clinically oriented study.

• We thank the Referee for this comment, but would like to draw his attention to the analysis in which we looked at clinical outcomes of HIV/AIDS individuals with AED usage by determining immunologic and virologic markers as well as liver toxicity (Figure 3-4 and Supplementary Figure 1). In conjunction with indication, frequency and cumulative exposure of AEDs (Figure 3), we feel that a significant portion of this manuscript contains clinically-oriented information.

2. Patients were on additional medications; the effects of concomitant medications in 2 groups were not looked into.

• The Referee raises an excellent point with regard to concomitant medications. Other drugs e.g. interleukin-2, cyclosporine and minocycline might have the effects on proliferation of CD4+ T cells or HIV/SIV replication. Because there are
few patients, if any, in our cohort whom received these drugs at the same time as AED therapy, their effects were not considered relevant to this study.

3. The effect dosage of each AEDs and especially with respect to its serum levels need to be studied?

• We thank the Referee for highlighting this important point and agree with him that the difference in AED dosage and its serum levels might affect the toxicity and immune benefits of AEDs. In this study, AEDs were prescribed for treating neurological/neuropsychiatric disorders at various dosages to achieve therapeutic blood levels. As mention in page 14 of the discussion, the blood levels of AEDs e.g. valproate, carbamazepine and phenytoin were monitored and dosages were adjusted to therapeutic levels as required. Importantly, this is the first study of AED cumulative dosing reported to date.

4. How do he authors conclude that rise in CD count was due to SVA or Ca blockers and not due to cART?

• The Referee points out an important limitation of this study. Because HIV-1 infected individuals received both cART and AEDs, we could not conclude that AEDs directly increased the levels of CD4+ T cells. However, we have attempted to control for these variables through the uniformity of cART regimens used in our cohort. As discussed on page 16, we highlight several mechanisms through which sodium channel and calcium channel blocking AEDs contribute to the rise in CD4+ T cell levels. Our results in conjunction with other recent reports (Ances et al, J Neurovirol 2006; Siliciano et al, J Inf Dis, 2007; Sagot-Lerolle et al, AIDS 2008) indicated that valproate had no immune or virologic benefits (Figure 4) with higher liver toxicity in aviremic patients (Figure 3E). Therefore, other AEDs e.g. gabapentin or carbamazepine should be considered as adjunct therapies to treat neuropathic pain or other neuropsychological disorders in HIV-infected individuals.

5. There are previous studies which show effect on AEDs on viral replication itself. These effect might be also contributing the finding either directly or indirectly.

• We agree with the Referee that AEDs could have direct effects on viral replication. Previous studies reported that chronic exposure of T cell lines to phenytoin could inhibit HIV-1 p24 expression (Cloyd et al, Virology 1989) while valproate induced or suppressed HIV-1 replication depending on cell types (Withrrow et al, AIDS Res Hum Retroviruses 1997). Similar to Robinson and colleagues’ study (J Neurovirol 2006) in lymphocyte cell lines, we observed that phenytoin, gabapentin and valproate did not decrease HIV-1 replication in primary human blood lymphocytes at Days 2 to 4 post-infection and did not reduce HIV-1 viral load at 6 and 12 month post-AED use. In addition, recent clinical studies reported no virologic benefits of valproate in HIV-1 infected individuals (Ances et al, J Neurovirol 2006; Siliciano et al, J Inf Dis, 2007; Sagot-Lerolle et al, AIDS 2008). We have cites these reports in the current version of the manuscript.