Author’s response to reviews

Title: Cryptococcal antigenemia is associated with meningitis or death in HIV-infected adults with CD4 100-200 cells/mm3

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Reviewer 1: Major Comments:

1) The authors showed the persons developed Meningitis due to Cryptococcal infections. Among HIV infected persons with 100-200 or <100 CD4 T cell counts per mm3, are there any other opportunistic infections. If so, authors may need to check the mortality rate among those infected with cryptococcal infection along with other opportunistic infections or exclusively with cryptococcal infections. Due to loss of immunity among HIV infected persons with <100 CD4 T cell counts, tuberculosis infection is very common among these individuals. Were they tested for tuberculosis infection. Did it contribute to the mortality rate? These are very important questions that needs to be addressed to detail.

Response: Thank you for this feedback. All participants underwent the WHO four-symptom screen at study enrollment, and followed the usual South African care pathway if they screened positive. Subsequent follow up visits and data gathering included the results of sputum testing, if indicated. We agree that patients at risk for cryptococcal meningitis are also at risk for TB infection, and that the inability to clarify cause of death for most participants is a limitation of our study. We have updated the discussion and methods to reflect this.

Methods, line 76:
“Participants also underwent the WHO 4-symptom screen for tuberculosis (TB).”

Discussion, lines 184-188

“PLWH are at increased risk of multiple opportunistic infections, not just cryptococcal meningitis. In particular, KwaZulu-Natal has a high rate of TB and HIV/TB co-infection. While we did assess TB symptoms at the time of enrollment, we were unable to reliably assess for development TB-related mortality. Overall, our findings are limited by the inability to confirm cause of death in all participants.”

Minor Comments:

1) The manuscript has several language errors and need to be corrected.

2) The font size of labels on the x and y axes need to be increased.

Response: We appreciate this feedback. We have performed additional review of the grammar and language in the manuscript, and adjusted the font size as requested.

Reviewer 2: I have one fundamental issue with the authors conclusions,

Among the 209 participants included in the group with CD4 count 100-200 cells/mm$^3$, none of the CrAg positive (n=4) and CrAg negative participants (n=205) developed cryptococcal meningitis during the period of follow-up. However, mortality was reported in 2/4 CrAg positive and 11/205 CrAg negative participants. This data was obtained from the South African death registry. Based on the information provided it is unclear that the increased mortality observed in this group is related to cryptococcal meningitis. Given the absence of such an association it is unclear that even if CrAg screening is implemented in this group of people, it would have any benefit to reduce morbidity and mortality.

Response: We appreciate this feedback, and recognize that one limitation of using South African death registry data is the inability to confirm cause of death in many of these cases. Certainly, PLWH with moderate immunosuppression are at increased risk of mortality from many causes including, but not limited to, cryptococcal meningitis. Obtaining a gold standard lumbar puncture to look for CrAg was not possible in our study cohort. However, we feel that these results still bear significance, as they demonstrate that CrAg positivity helps demonstrate a group of individuals at high risk for mortality. While not conclusive, these findings suggest that this group of PLWH with CD4 100-200 cells/mm$^3$ deserves further examination. We have updated the discussion section to further expand on this limitation, and made a more explicit recommendation for further study and re-examination of existing data to evaluate for similar result in PLWH with CD4 100-200 cells/mm$^3$. 
Discussion, lines 180-188:

“We used a combined outcome of death or confirmed cryptococcal meningitis in our study, although we suspect many of the deaths identified through searching the national registry could have been due to death from cryptococcal meningitis despite the participants not presenting for further evaluation. PLWH are at increased risk of multiple opportunistic infections, not just cryptococcal meningitis. In particular, KwaZulu-Natal has a high rate of TB and HIV/TB co-infection, and while we did assess TB symptoms at the time of enrollment, we are unable to reliably assess for development of TB or TB-related mortality. Overall, our findings are limited by the inability to confirm cause of death in all participants.”

Minor points:

The acronym used for "people living with HIV" should be uniform across the manuscript. For example, PLHIV is used in abstract, while PLWH is used in the remainder of the manuscript.

Response: We appreciate this feedback, and have adjusted the acronym used in the abstract to ensure continuity.