



RESEARCH ARTICLE

**REVISED** **A secondary analysis of depression outcomes from a randomized controlled trial of adjunctive sertraline for HIV-associated cryptococcal meningitis [version 2; peer review: 2 approved with reservations]**

Previous title: The effect of sertraline on depression and associations with persistent depression in survivors of HIV-related cryptococcal meningitis

Sarah M. Lofgren <sup>1,2</sup>, Sruti S. Velamakanni<sup>2</sup>, Katherine Huppler Hullsiek <sup>3</sup>, Ananta S. Bangdiwala <sup>3</sup>, Alice Namudde<sup>2</sup>, Abdu K. Musubire <sup>2</sup>, Edward Mpoza<sup>2</sup>, Mahsa Abassi<sup>1,2</sup>, Katelyn A. Pastick <sup>1</sup>, Edwin Nuwagira<sup>4</sup>, Emily E. Evans<sup>4</sup>, Radha Rajsasingham<sup>1</sup>, Darlisha A. Williams<sup>2</sup>, Conrad Muzoora<sup>4</sup>, Fiona V. Creswell <sup>2</sup>, Joshua Rhein <sup>1,2</sup>, David J. Bond<sup>5</sup>, Noeline Nakasujja<sup>2,6</sup>, David B. Meya <sup>2</sup>, David R. Boulware <sup>1</sup>,  
Adjunctive Sertraline for the Treatment of HIV Associated Cryptococcal Meningitis (ASTRO-CM) team)

<sup>1</sup>Medicine, Division of Infections Diseases and International Medicine, University of Minnesota, Minneapolis, MN, 55455, USA

<sup>2</sup>Infectious Diseases Institute, Makerere University, Kampala, Uganda

<sup>3</sup>School of Public Health, Division of Biostatistics, University of Minnesota, Minneapolis, MN, 55455, USA

<sup>4</sup>Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

<sup>5</sup>Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis, MN, 55455, USA

<sup>6</sup>Psychiatry, Makerere University, Kampala, Uganda

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### Abstract

**Background:** Depression is a risk factor for worse HIV outcomes in persons living with HIV/AIDS, including engagement-in-care, HIV medication adherence, and retention-in-care. Depression has a prevalence of more than three times as high as in the general population. Despite this, there are few randomized studies of antidepressants in HIV-infected Africans, including those with opportunistic infections.

**Methods:** We enrolled 460 HIV-infected Ugandans with cryptococcal meningitis into a randomized clinical trial of adjunctive sertraline vs placebo (2015-2017). We defined depression using the Center for Epidemiologic Studies Depression Scale (CES-D) score of >15, and

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1. **Nathan Ford**, World Health Organization,

severe depression as >26 at one and three months after meningitis diagnosis and initiation of treatment. We evaluated the relationship between sertraline and depression, as well as associations with persistent depression, at three months.

**Results:** At one- and three-months post meningitis diagnosis, 62% (108/174) and 44% (74/169) of all subjects had depression (CES>15), respectively. At three months, sertraline-treated subjects had consistent risk for depression as placebo-treated subjects but were significantly less likely to have severe depression (CES>26) (OR 0.335; 95%CI, 0.130-0.865). Of those with depression at one month, sertraline-treated subjects were less likely than placebo-treated subjects to be depressed at three months ( $p=0.05$ ). Sertraline was the only factor we found significant in predicting persistent depression at three months among those with depression at one month.

**Conclusions:** Depression is highly prevalent in HIV-infected persons who have survived cryptococcal meningitis. We found that sertraline is associated with a modest reduction in depression in those with depression at baseline and a significant decrease in severe depression.

### Keywords

Depression, HIV, sertraline, Antidepressive Agents, Depressive Disorder, Treatment-Resistant, biomarkers

Geneva, Switzerland

2. **Melanie Amna Abas** , King's College  
London, London, UK

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Sarah M. Lofgren ([lofg0020@umn.edu](mailto:lofg0020@umn.edu))

**Author roles:** **Lofgren SM:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Velamakanni SS:** Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; **Huppler Hullsiek K:** Formal Analysis, Methodology, Project Administration, Writing – Review & Editing; **Bangdiwala AS:** Data Curation, Formal Analysis, Writing – Review & Editing; **Namudde A:** Investigation, Writing – Review & Editing; **Musubire AK:** Investigation, Writing – Review & Editing; **Mpoza E:** Investigation, Writing – Review & Editing; **Abassi M:** Investigation, Writing – Review & Editing; **Pastick KA:** Data Curation, Investigation, Writing – Review & Editing; **Nuwagira E:** Data Curation, Project Administration, Writing – Review & Editing; **Evans EE:** Data Curation, Investigation, Project Administration, Writing – Review & Editing; **Rajsasingham R:** Writing – Review & Editing; **Williams DA:** Data Curation, Investigation, Project Administration, Writing – Review & Editing; **Muzoora C:** Investigation, Writing – Review & Editing; **Creswell FV:** Investigation, Writing – Review & Editing; **Rhein J:** Conceptualization, Investigation, Methodology, Writing – Review & Editing; **Bond DJ:** Writing – Original Draft Preparation, Writing – Review & Editing; **Nakasujja N:** Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Meya DB:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Boulware DR:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Resources, Software, Supervision, Writing – Review & Editing;

**Competing interests:** Dr. Boulware collaborates with multiple pharmaceutical companies making novel antifungal medicines for cryptococcal meningitis in public-private research partnerships, without any financial interests or payments from these companies. Gilead has provided grants and Ambisome antifungal medication to the Infectious Disease Institute in Uganda and Meningitis Foundation for cryptococcal meningitis-related research. However, no investigators have financial interests or have received funding from Gilead.

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**REVISED Amendments from Version 1**

Our reviewers were concerned that we did not have it in the proper context for an analysis of depression from a study done with sertraline as an antifungal. As such, we changed the title from "The effect of sertraline on depression and associations with persistent depression in survivors of HIV-related cryptococcal meningitis" to "A secondary analysis of depression outcomes from a randomized controlled trial of adjunctive sertraline for HIV-associated cryptococcal meningitis." In the Abstract, we made the HIV effects of depression more specific. In the Introduction, we added a paragraph about the sequelae of cryptococcal meningitis. In the Methods, we added details about sertraline dosing in this study. We did some grammatical polishing throughout. In the Discussion, we added a paragraph about sertraline dosing in the study compared to the usual dosing for depression. We added context to depression treatment in Africa. Finally, we moved a paragraph about antidepressant therapy among people with cryptococcal meningitis to the end of the Discussion.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

In persons living with HIV/AIDS, the prevalence of depression is up to three times more common than in the general population<sup>1,2</sup>, making depression one of the most common neuropsychiatric complications in these individuals<sup>3</sup>. The underdiagnosis of major depression in people with HIV undoubtedly contributes negatively to individuals' overall well-being<sup>4</sup>. People diagnosed with depression and HIV infection often have poorer clinical and HIV outcomes than those diagnosed with HIV infection without depression<sup>5,6</sup>. Treatment for depression in people living with HIV/AIDS utilizes the same mainstays for treatment of depression as in the general population: antidepressant medication and talk therapy<sup>7</sup>. However, there is surprisingly little data on the efficacy of depression therapies in individuals with HIV<sup>8–10</sup>.

Additionally, people with meningitis are known to have long-term sequelae such as deafness<sup>11,12</sup>. However, there is a paucity of data about the prevalence of psychiatric consequences among people following meningitis, much less the treatment of said disease<sup>13,14</sup>. Cryptococcal meningitis is a complex condition as people generally have advanced immunosuppression such as advanced HIV to be susceptible<sup>15</sup>. Given cryptococcal meningitis is highly prevalent at 220,000 cases a year, more information is needed about the long-term consequences of survivors.

Here we present data on the rates of depression in participants in a cryptococcal meningitis trial, the effects of sertraline on said depression, and risk factors for persistent depression in this cohort. This work is a secondary analysis of a randomized, double-blind, placebo-controlled clinical trial that investigated the utility of adjunctive sertraline as a putative antifungal medicine among persons with AIDS and cryptococcal meningitis, Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (ASTRO-CM)<sup>16</sup>. The trial assessed depression via the Center for Epidemiologic Studies Depression

Scale (CES-D) as a secondary endpoint. We sought to evaluate the effect of sertraline on the prevalence and severity of depression in cryptococcal meningitis survivors from the randomized trial. We also assessed risk factors for and the prevalence of depression among pooled prospective cohorts from 2010–2017, including ASTRO-CM, among Ugandans surviving cryptococcal meningitis.

**Methods**

For this paper, we used data from the ASTRO-CM randomized trial<sup>16</sup>. In ASTRO-CM, we prospectively consented 460 HIV-infected adults who tested positive for cerebrospinal fluid (CSF) cryptococcal antigen at Mulago National Referral Hospital in Kampala, Uganda from March 2015 to May 2017. All participants received intravenous amphotericin B deoxycholate (0.7–1.0 mg/kg/day) with oral fluconazole 800mg/day. Participants were treated for meningitis as an inpatient for at least one week. They were randomized to receive either adjunctive sertraline or placebo; 229 participants started with 400mg/day of sertraline, while 231 received the placebo<sup>16</sup>. Sertraline at 400mg/day was continued for 2 weeks, decreased to 200 mg/day for 12 weeks, and then tapered off over 3 weeks. The dosing was for antifungal treatment and double the maximum dose for depression. Depression scores were evaluated at one and three months using the CES-D scale, a self-reported questionnaire comprised of 20 items representing overall mood and feelings. Given how ill participants are with cryptococcal meningitis, they were not screened for depression as an inpatient or otherwise prior to their one-month outpatient visit. Therefore, we defined depression as a CES-D score of >15 on a 0 to 60-point total scale<sup>17,18</sup>. Mulago National Referral Hospital (MREC 429) and the University of Minnesota Institutional Review Boards (1304M31361) approved the protocol. All participants or their surrogates provided written informed consent.

We compared subjects with depression (CES-D scores >15) to subjects without depression (CES-D score 0–15) on demographic factors, including gender and age, clinical characteristics, such as viral load, fungal burden, antiretroviral medications, mental status based on Glasgow Coma Scale, and persistent depression. We compared continuous variables using Mann-Whitney U and categorical variables using Chi-square. We repeated the analysis in the sub-group of subjects with severe depression using the CES-D cutoff  $\geq 26$ <sup>19</sup>. We further examined the effect of sertraline versus placebo within the ASTRO-CM randomized trial alone (n=460) regardless of depression status at one month. Finally, we evaluated the data as might be done in an antidepressant drug trial looking at those depressed at baseline (one month) and the change in CESD score, response rate, and remission rates.

We next looked at demographic associations with persistent depression at three months. We first evaluated this in the ASTRO-CM randomized trial alone, followed by a sensitivity analysis for baseline associations of persistent depression. In this sensitivity analysis, we included two other cohorts of cryptococcal meningitis survivors, which also evaluated participants for clinical depression. One of these cohorts included 172 subjects enrolled as a part of the ASTRO-CM

pilot phase II trial. In this pilot study, participants received varying doses of sertraline (100 mg to 400 mg daily) for the first two weeks (n=172), followed by 200 mg sertraline daily until 3 months when it was subsequently tapered<sup>20</sup>. The second cohort, the Cryptococcal Optimal Antiretroviral therapy Timing (COAT) trial, enrolled 177 subjects and assessed early versus deferred initiation of HIV therapy; participants did not receive sertraline in this cohort<sup>21</sup>. Finally, we calculated odds ratios to evaluate for risk of depression. Both the analysis and graphing were performed using Microsoft Excel version 16 (Redmond, WA) and IBM SPSS Statistics version 26 (Armonk, NY).

## Results

We enrolled 460 persons with a first episode of cryptococcal meningitis into the ASTRO-CM sertraline randomized trial. As previously reported, the median age of the enrolled participants was 35 years<sup>16</sup>. The median CD4 count was 15 cells/mm<sup>3</sup>, and 41% of the enrolled subjects were women. Baseline characteristics are shown in Table 1<sup>22</sup>. There were

no significant differences at baseline by randomized groups. Overall, 273 (59%) survived more than a month, and 234 (51%) survived more than 3 months.

### Differences between those screened and unscreened for depression

We selected those who survived for one month and compared those who were screened for depression and those not screened. Overall, 273 (59%) had survived >1 month, and 234 (51%) survived through >3 months. Of subjects who survived one month, 174 (64%) had depression screening performed at one month and 169 (72%) at three months.

Those in ASTRO-CM not screened for depression at three months, but were still alive, had higher mortality (p<0.001), a higher CSF opening pressure >200 mmH<sub>2</sub>O (p=0.024), and had a higher depression score at one month (p=0.025) compared to those screened for depression at three months. These findings suggest that the reason for not screening for depression was illness-related.

**Table 1. Baseline characteristics in randomized Adjunctive Sertraline for the Treatment of HIV Associated Cryptococcal Meningitis (ASTRO-CM) Trial.**

	Placebo (N=231) Median (IQR) or N(%)	Sertraline (N=229) Median (IQR) or N(%)	P-value*
<b>Demographics</b>			
Age, years	35 (30-41)	35 (29-40)	0.234
Women	37.7%	97 (42.4%)	0.304
CD4 cell count, cells/mm <sup>3</sup>	13 (6-41)	17 (7-47)	0.362
Receiving ART	48.1%	48.9%	0.854
<b>Baseline CSF Analysis</b>			
Opening pressure, mm H <sub>2</sub> O	270 (180-410)	248 (170-380)	0.172
Opening pressure >200 mm H <sub>2</sub> O	68.5%	60.7%	0.100
Cryptococcal culture, log <sub>10</sub> CFU/mL	4.82 (3.63-5.55)	4.78 (3.56-5.62)	0.946
Sterile culture	6.6%	11.0%	0.098
CSF white-cell count >5 cells/mm <sup>3</sup>	66.2%	58.4%	0.088
CSF protein, mg/dL	42 (22-100)	47 (23-106)	0.576
Number of lumbar punctures	4 (2-6)	4 (2-6)	0.858
2 <sup>nd</sup> lumbar puncture opening pressure, mmH <sub>2</sub> O**	260 (140-400)	260 (180-400)	0.859
Day 14 CSF opening pressure, mmH <sub>2</sub> O	200 (130-300)	200 (150-300)	0.539

\*P-values from continuous variables calculated with Mann-Whitney U, p-values from categorical variables calculated with Pearson Chi-square (2-sided).

\*\*2<sup>nd</sup> LP at day 2-5 and N=199.

IQR= Interquartile Range, ART= Antiretroviral Therapy, CSF= Cerebrospinal Fluid.

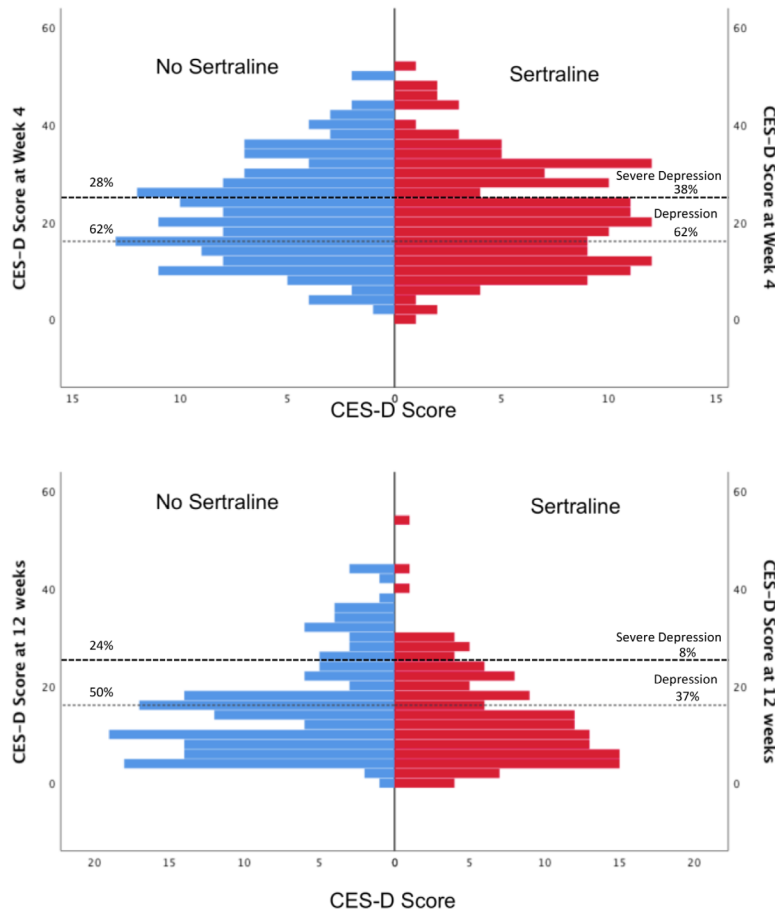
### Impact of sertraline on depression

We screened 174 participants for depression at one or three months using the CES-D scoring criteria. At one and three months, 62% (108/174) and 44% (74/169) of all subjects had depression. At three months, those receiving sertraline were non-significantly more likely to be depressed compared to those receiving placebo (37% vs. 64%,  $p=0.091$ ).

We assessed subgroups of those who may have benefited from sertraline. Depression categories were subdivided into no

depression (CES-D <16), moderate depression (CESD 16–25), and severe depression (CES-D ≥26). Those receiving sertraline were significantly less likely to have severe depression at three months versus moderate or no depression than those not on sertraline ( $p=0.030$ ).

In [Figure 1](#), a population pyramid compares the CES-D score based on sertraline or placebo at one and three months. Sertraline had little effect on depression at one month, with no significant differences between groups.



Depression Scores	N	Placebo	N	Sertraline	P-value	Odds Ratio
CES-D 1 month	90	20 (13-28)	84	20 (11-29)	0.960	
Depressed at 1 month	56	62.2%	52	61.9%	0.966	0.995 (0.615-1.609)
Severe Depression at 1 month	25	27.8%	32	38.1%	0.147	1.371 (0.751-2.503)
CES-D 3 months	95	15 (7-25)	74	12 (7-19)	0.074	
Depressed at 3 months	47	49.5%	27	36.5%	0.091	0.738 (0.420-1.294)
Severe Depression at 3 months	23	24.2%	6	8.1%	<b>0.006</b>	<b>0.335 (0.130-0.865)</b>

Numbers are n (%) and median (IQR). P-values by non-parametric Mann Whitney U or by Chi-square.

**Figure 1.** Population Pyramid Comparing CES-D score by sertraline or placebo at one and three months.

There was a similar percentage of people with depression receiving sertraline compared with placebo (62.2% vs. 61.9%,  $p=0.966$ ), and more with severe depression (38.1% vs. 27.8%  $p=0.147$ ). However, by three months, there were lower rates of depression in individuals receiving sertraline versus those receiving placebo (36.5% vs. 49.5%,  $p=0.091$ ), though not statistically significant. At three months, significantly fewer participants receiving sertraline had severe depression compared with those receiving placebo (8.1% vs. 24.2%,  $p=0.006$ ).

Outside a clinical trial using sertraline as an antifungal, a patient would typically only be prescribed an anti-depressant as an outpatient. Therefore, we examined those 135 who had depression (CES-D  $\geq 16$ ) at one-month post meningitis diagnosis, which is the time of entering outpatient HIV care. We also evaluated the baseline (one month) to endpoint (three months) change in CES-D score for sertraline versus placebo. We found that the median (IQR) change was 8 (-2.5–19.5) for sertraline versus 5 (-2–12),  $p=0.095$ . We also evaluated the response rate of 50% improvement in CES-D score from one to three months. We found that the response rate for sertraline was 50% compared to 33.8% for placebo ( $p=0.056$ ). As stated above, the percentage of resolved depression was not statistically better for sertraline than placebo ( $p=0.091$ ).

#### Baseline factors associated with persistent depression at three months in ASTRO-CM sertraline randomized control trial

Factors associated with persistent depression at three months in the randomized ASTRO-CM sertraline trial were evaluated (Table 2). A higher percentage of women (44 (59.5%)) and those with Glasgow coma scale  $<15$  (33 (44.6%)) trended towards being more likely to be depressed (CES-D  $>15$ ) than men and those with Glasgow coma scale of 15. Depression at one month was not associated with depression at three months (65% vs. 55%,  $p=0.286$ ).

#### Baseline factors associated with persistent depression at three months in combined cohorts

Factors associated with persistent depression at three months were examined from the combined cohorts of 883 participants (2010–2017) to determine if our findings were generalizable. In the combined cohorts, 66.3% and 38.5% of subjects had depression at one and three months, respectively. Those with depression at three months were less likely to be from Kampala (82.5% vs. 96.2%  $p<0.001$ ) and were more likely to have a Glasgow Coma Score (GCS)  $<15$  at entry (37.7% vs. 26.5%,  $p=0.043$ ). Sertraline was not associated with a difference in depression (41.2% vs. 48.4%,  $p=0.231$ ) in the combined cohorts.

## Discussion

This analysis of participants with cryptococcal meningitis reveals that sertraline given regardless of depression status in the ASTRO-CM sertraline randomized trial did not significantly reduce depression. The change in CESD, response rate, and remission rate were not significantly better in sertraline compared to placebo among all comers. Sertraline significantly

lowered the prevalence of severe depression in those recovering from cryptococcal meningitis for all-comers. Further, sertraline was associated with significantly less depression at three months in those with depression at one month.

The percentage of participants with depressive symptoms at one month was 67% in ASTRO-CM, which likely represents major depression, acute adjustment disorder, pain, severe illness, and appropriate anxiety. At three months, the percentage of participants with depressive symptoms was 44% in ASTRO-CM. While this still is affected by pain, illness, and other factors, it is likely a better measure of depression symptoms than other causes. For this reason, we based our depression outcomes on three and not one-month outcomes.

The study participants had multiple reasons to have depressive symptoms at one and three months. As the subjects had just survived a critical illness, they were still quite ill with advanced HIV, and many had yet to start or re-start HIV medication. Most participants had not worked for weeks to months, and many had just disclosed their HIV status to their loved ones for the first time. In the open wards of the hospital, the individuals in the study knew other participants who had died and understood better than most, the mortality associated with cryptococcal meningitis. Anecdotally, our staff found that counseling and social support helped participants considerably.

In the combined cohorts, individuals from areas outside of Kampala and those with a GCS  $<15$  were found to have higher rates of depression. This association with location could be due to limited financial resources and the inability to access necessary healthcare in outlying areas. In addition, those with GCS  $<15$  were sicker, which may be associated with more symptoms such as headaches and needing more frequent lumbar punctures. However, there was no variation in the fungal burden between the groups.

Participants who had their CES-D measured in this study were well enough to attend outpatient clinic and answer survey questions. Not only did these participants have lower fungal burdens, but they were also less likely to have altered mental status and had decreased mortality rates. This selection bias of mortality for those screened for depression is a limitation of this study but one true of all studies with critically ill individuals.

The dosage of sertraline used in this study was 400mg/day for two weeks, followed by 200 mg/day for 12 weeks, then tapered off over 3 weeks. The recommended starting dose of sertraline for depression is 50 mg/day with a general maximum recommended dose of 200 mg/day<sup>23</sup>. Sertraline has been shown to have dose dependence effects, with some studies showing short-term use of 400 mg with good response on depression<sup>24</sup>. We used 400 mg/day for the treatment of Cryptococcus, not for depressive symptoms<sup>16</sup>. These patients were monitored as inpatients over at least one week, and sertraline was generally well tolerated. Since the efficacy of sertraline is generally over 4–6 weeks, we would expect some signs of reduced depression at our 4-week timepoint and certainly at 3 months<sup>24</sup>.

**Table 2. Factors associated with persistent depression at three Months in Randomized Adjunctive Sertraline for the Treatment of HIV Associated Cryptococcal Meningitis (ASTRO-CM) Trial.**

	Depression CES-D $\geq$ 16 (N=74) Median (IQR)	No Depression CES-D <16 (N=95) Median (IQR)	P-value*
<b>CES-D Score at three months</b>	23 (18-30)	8 (4-11)	----
<b>Demographics</b>			
Age, years	34.5 (29.0-40.0)	35.0 (29.0-38.0)	0.313
Women	40.5%	28.4%	0.098
<b>Clinical characteristics</b>			
Glasgow Coma Scale Score <15	44.6%	31.6%	0.083
CD4 cell count, cells/mm <sup>3</sup>	16 (7-51)	19 (8-52)	0.996
Receiving ART	40.5%	49.5%	0.247
<b>Baseline CSF Analysis</b>			
Opening pressure, mm H <sub>2</sub> O	265 (180-370)	260 (200-340)	0.919
Opening pressure >200 mm H <sub>2</sub> O	64.5%	73.3%	0.254
Cryptococcal culture, log <sub>10</sub> CFU/mL	4.6 (3.4-5.3)	4.7 (3.4-5.3)	0.802
Sterile CSF cryptococcal culture	6.8%	9.5%	0.542
CSF white-cell count $\geq$ 5 cells/mm <sup>3</sup>	45.7%	44.2%	0.848
CSF protein, mg/dL	50.0 (20-141.5)	49.5 (20.8-120.0)	0.638
<b>Follow-up CSF Analysis</b>			
Day 14 CSF Opening pressure >200	43.2%	51.9%	0.393
<b>Depression at One Month</b>			
CES-D Score	20 (14-28)	18 (11-27)	0.368
% Depressed (CES-D >16)	64.5%	54.9%	0.286

\*P-values from continuous variables calculated with Mann-Whitney U, p-values from categorical variables calculated with Pearson Chi-Square.

CES-D= Center for epidemiologic studies depression scale, IQR= Interquartile Range, ART= Antiretroviral Therapy, CSF= Cerebrospinal Fluid

There is a limited amount of data for the treatment of depression in people living with HIV globally<sup>25,26</sup>. These interventions are varied, and include therapy and antidepressant medications and showed short-term efficacy but little long-term data<sup>25</sup>. The interventions are particularly limited in Africa<sup>7,8</sup>. In South Africa, Hoare *et al.* conducted a randomized controlled trial of escitalopram in those with HIV-associated depression<sup>27</sup>. The results of this study were null; however, they only used a starting dose of escitalopram and did not increase the dose or change SSRIs. A recent Cochrane review

found some data demonstrating that SSRIs were effective in people with HIV, but none of these studies took place in Africa, and the data were inadequate<sup>8</sup>. Further work is needed given the large numbers of people from African countries living with HIV and the high prevalence of depression in this population<sup>28-31</sup>.

Only a few preexisting studies have previously evaluated depression and cryptococcal meningitis. We found one case report of an HIV-positive individual with depression

associated with cryptococcal meningitis<sup>20</sup>, a case series of HIV-negative individuals with cryptococcal meningitis<sup>21</sup>, and two case reports where HIV-statuses were not revealed<sup>22,23</sup>. We believe this is the first large study of depression following cryptococcal meningitis diagnosis, and the first randomized, controlled trial of a selective sertraline reuptake inhibitor (SSRI) in those with cryptococcal meningitis.

### Limitations

In this study, the participants evaluated were seriously ill with cryptococcal meningitis and AIDS. They were given high-dose sertraline at enrollment but had depression only measured at one and three months, and one month was taken as the baseline measurement. Many individuals died in the first two weeks. Thus, those individuals were not included in one or three-month measurements. CES-D was not measured at baseline, given the prevalence of decreased GCS <15 or more subtle signs of altered mental status, as well as overall poor health, such as headache, nausea, and vomiting. This study may not have generalizability to those without meningitis; however, this is one of the first placebo-controlled randomized control trials of SSRIs in Africans with HIV.

### Conclusion

Depression has a high prevalence in survivors of cryptococcal meningitis. We found that sertraline was non-significantly associated with reduced depression in all-comers and significantly associated with severe depression in all-comers. Sertraline was significantly associated with reduced depression at 3 months among those depressed at 1 month. Larger

randomized, controlled trials are needed to examine depression in those with the general HIV population.

### Data availability

#### Underlying data

DRYAD: The effect of sertraline on depression and associations with persistent depression in survivors of HIV-related cryptococcal meningitis. <https://doi.org/10.5061/dryad.n5tb2rbtr><sup>22</sup>

This project contains the following underlying data:

- Combined\_CM\_Depression\_Database.xlsx (CM patient depression data)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

### Acknowledgments

We thank all of the research participants for their willingness to participate in this work. ASTRO-CM Team members include Lillian Tugume, Jane Francis Ndyetukira, Cynthia Ahimbisibwe, Florence Kugonza, Carolyne Namuju, Alisat Sadiq, Henry W Nabeta, James Mwesigye, Paul Kirumira, Michael Okirwoth, Andrew Akampurira, Tony Luggya, Julian Kaboggoza, Eva Laker, Leo Atwine, Davis Muganzi, Bilal Jawed, Matthew Merry, Anna Stadelman, Andrew Flynn, A. Wendy Fujita, Liliane Mukaremera, Bozena M. Morawski, Kabanda Taseera, and Kirsten Nielsen.

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# Open Peer Review

Current Peer Review Status: ? ?

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## Version 2

Reviewer Report 01 December 2022

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**Melanie Amna Abas**

Health Service and Population Research Department, King's College London, London, UK

Thanks to the authors for their revisions - the paper and is much improved.

However, I am still unclear if those who received sertraline differed from the placebo group in terms of physical health e.g. Glasgow coma score, or dose of amphotericin. And if so, if any of the physical health factors acted as confounders of the association between sertraline and depression outcome.

Can the authors comment?

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Depression, HIV. global mental health

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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## Version 1

Reviewer Report 27 June 2022

<https://doi.org/10.21956/wellcomeopenres.17997.r50426>

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**Melanie Amna Abas** 

Health Service and Population Research Department, King's College London, London, UK

This is a clinical trial of Sertraline being used as an adjunctive antifungal agent in people living with HIV in Uganda with cryptococcal meningitis. The authors conducted a secondary analysis to look at the potential benefit of Sertraline on depression.

- I would like the authors to comment on the validity of the CES-D in this Ugandan context.
- Please consider altering language to 'Ugandans' or people from an African country.
- Sertraline was being used as an adjunct antifungal. This should be made clear in the Abstract. I would like the authors to make it very clear if there is confounding by physical health - specifically, was there a greater change in meningitis-related outcomes in the sertraline arm which might account for the reduced depression?
- Sertraline was started and used at a much higher dose than used normally for depression. Please comment on this.

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

No

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Depression, HIV. global mental health

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 14 Nov 2022

**Sarah Lofgren**, University of Minnesota, Minneapolis, USA

*Thank you for your review and comments.*

From Reviewer:

This is a clinical trial of Sertraline being used as an adjunctive antifungal agent in people living with HIV in Uganda with cryptococcal meningitis. The authors conducted a secondary analysis to look at the potential benefit of Sertraline on depression.

1. I would like the authors to comment on the validity of the CES-D in this Ugandan context.

*Response 1. The CES-D was developed in 1971 in Israel and then compared in 1977 among individuals from Kansas City and Washington County, MD USA.<sup>1, 2</sup> It was used internationally by the WHO in 1994 among people living with HIV in Bangkok, Kinshasa, Munich, Nairobi, and Sao Paulo.<sup>3</sup> A pubmed search on 11/7/2022 gives 40 studies using the CES-D in Uganda, including a validation study for pregnant women in 2014 that found it suitable in that population compared to the MINI.<sup>4</sup>*

<https://pubmed.ncbi.nlm.nih.gov/?term=%28Center+for+Epidemiologic+Studies+Depression+Scale%29+AND+%28>

*Overall the CES-D has been widely used and is considered valid. We delivered the CES-D in the native language of Luganda by native Lugandan speakers. It was given orally by healthcare workers to reduce the concern of low literacy.*

2. Please consider altering language to 'Ugandans' or people from an African country.

*Response 2. We changed Africans to Ugandans in the abstract methods given these were who we enrolled. Further we changed the last sentence of the second to last paragraph in the discussion to "Further work is needed given the large numbers of people from African countries living with HIV and the high prevalence of depression in this population."<sup>5-8</sup>*

*However, we decided to leave Africans in 2 places - in the intro of the abstract and in the limitations as we were being concise and were pointing to a broader discussion of people from Africa, not just Uganda.*

3. Sertraline was being used as an adjunct antifungal. This should be made clear in the Abstract. I would like the authors to make it very clear if there is confounding by physical health - specifically, was there a greater change in meningitis-related outcomes in the sertraline arm which might account for the reduced depression?

*Response 3. We added adjunctive to the title. The first line of the abstract methods also says adjunctive.*

*Certainly, depression is tied to the clinical course. If you feel sick you will likely have depressive symptoms. However, sertraline did not improve the clinical course of the meningitis or reduce mortality.<sup>9</sup> In fact those who got sertraline had non-statistically significant increased mortality so this trial was stopped early for futility. Therefore, we think the impact on depressive symptoms was felt to be independent of the fungal meningitis course.*

4. Sertraline was started and used at a much higher dose than used normally for

depression. Please comment on this.

*Response 4. We added this paragraph as the 5<sup>th</sup> paragraph of the discussion: "The dosage of sertraline used in this study 400mg/day for two weeks, followed by 200 mg/day for 12 weeks, then tapered off over 3 weeks. The recommended starting dose of sertraline for depression is 50 mg/day with a general maximum recommended dose of 200 mg/day.<sup>10</sup> Sertraline has been shown to have dose dependence effects with some studies showing short-term use of 400 mg with good response on depression.<sup>11</sup> We used 400 mg/day for the treatment of Cryptococcus not for depressive symptoms.<sup>9</sup> These patients were monitored inpatient over at least one week and it was generally well tolerated. Since the efficacy of sertraline is generally over 4-6 weeks we would expect some signs of reduced depression at our 4 week timepoint and certainly at 3 months.<sup>11</sup>"*

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**Competing Interests:** None

Reviewer Report 19 April 2021

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### Nathan Ford

Department HIV and Global Hepatitis Programme, World Health Organization, Geneva, Switzerland

#### Title

Please specify the study design in the title.

#### Abstract

"Depression is a risk factor for worse outcomes in persons living with HIV/AIDS..." - What type of outcomes?

This study is not about persons living with HIV/AIDS generally – see comment about the introduction.

#### Introduction

This study is not about people with chronic illness. It is a specific population. Please rewrite the introduction to focus on the population addressed by this study.

#### Results

"The median CD4 count was 15 cells/mcL" - Please use standard units: mm<sup>3</sup>, as used in table 1.

#### Discussion

Please compare the dosing of Sertraline in this study with usual dosing/frequency as an antidepressant. Also, what is known about time to effectiveness. Given that it generally takes 4-6 weeks to work, how would this be anticipated to affect the outcomes of this trial?

There is a section in the discussion summarizing data on use of antidepressants in Africans living with HIV. Please expand to summarize what is known about use of antidepressants in people living with HIV in general. Given what is known, is sertraline a rational choice? Also, please summarize other evidence-based interventions for treating depression among people

living with HIV, including in Africa (e.g. PMID 32035035<sup>1</sup>).

### References

1. Nakimuli-Mpungu E, Musisi S, Wamala K, Okello J, et al.: Effectiveness and cost-effectiveness of group support psychotherapy delivered by trained lay health workers for depression treatment among people with HIV in Uganda: a cluster-randomised trial. *Lancet Glob Health*. **8** (3): e387-e398 [PubMed Abstract](#) | [Publisher Full Text](#)

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HIV epidemiology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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## Comments on this article

### Version 1

Author Response 07 Nov 2022

**Sarah Lofgren**, University of Minnesota, Minneapolis, USA

Response to Reviewer 1 Comments. Thank you for this kind review. We appreciate your time and hope these edits address your concerns.

## 1. Title

Please specify the study design in the title.

*Response 1.* Thank you, we changed the title to: A secondary analysis of depression outcomes from a randomized controlled trial of adjunctive sertraline for HIV-associated cryptococcal meningitis

## Abstract

1. "Depression is a risk factor for worse outcomes in persons living with HIV/AIDS..." - What type of outcomes?

*Response 2.* We changed the sentence to "Depression is a risk factor for worse HIV outcomes in persons living with HIV/AIDS including engagement-in-care, HIV medication adherence, and retention-in-care. Depression has a prevalence of more than three times as high as in the general population."

1. This study is not about persons living with HIV/AIDS generally – see comment about the introduction.

*Response 3.* We added an ending to the last sentence of the abstract intro: "Despite this, there are few randomized studies of antidepressants in HIV-infected Africans, including those with opportunistic infections." We agree that this is a complex sample with CNS infection. However, we think there remains value generally to people with HIV and depression given the paucity of data of antidepressants for depression in adults with HIV.<sup>1</sup>

## Introduction

1. This study is not about people with chronic illness. It is a specific population. Please rewrite the introduction to focus on the population addressed by this study.

*Response 4.* I removed the first two sentences to make it more specific to HIV and added a paragraph about meningitis to make it more specific.

## Results

1. "The median CD4 count was 15 cells/mcL" - Please use standard units: mm<sup>3</sup>, as used in table 1.

*Response 5.* This was done.

## Discussion

1. Please compare the dosing of Sertraline in this study with usual dosing/frequency as an antidepressant. Also, what is known about time to effectiveness. Given that it generally takes 4-6 weeks to work, how would this be anticipated to affect the outcomes of this trial?

*Response 6.* The dosage of sertraline used in this study 400mg/day for two weeks, followed by 200



mg/day for 12 weeks, then tapered off over 3 weeks. The recommended starting dose of sertraline for depression is 50 mg/day with a general maximum recommended dose of 200 mg/day.<sup>2</sup> Sertraline has been shown to have dose dependence effects with some studies showing short-term use of 400 mg with good response on depression.<sup>3</sup> We used 400 mg/day for the treatment of Cryptococcus not for depressive symptoms.<sup>4</sup> These patients were monitored inpatient over at least one week and it was generally well tolerated. Since the efficacy of sertraline is generally over 4-6 weeks we would expect some signs of efficacy at our 4 week timepoint and certainly at 3 months.<sup>3</sup>

1. There is a section in the discussion summarizing data on use of antidepressants in Africans living with HIV. Please expand to summarize what is known about use of antidepressants in people living with HIV in general. Given what is known, is sertraline a rational choice? Also, please summarize other evidence-based interventions for treating depression among people living with HIV, including in Africa (e.g. PMID 320350351).

*Response 7.* We edited that paragraph and included a discussion that included reviews of interventions of individuals with HIV in Africa including the study referenced. "There is a limited amount of data for the treatment of depression in people living with HIV globally.<sup>25, 26</sup> These interventions are varied including therapy and antidepressant medications and showed short-term efficacy but little long term data.<sup>25</sup> The interventions are particularly limited in Africa.<sup>7, 8</sup> In South Africa, Hoare *et al.* conducted a randomized controlled trial of escitalopram in those with HIV-associated depression.<sup>27</sup> The results of this study were null; however, they only used a starting dose of escitalopram and did not increase the dose or change SSRIs. A recent Cochrane review found some data demonstrating that SSRIs were effective in people with HIV, but none of these studies took place in Africa, and the data were inadequate.<sup>8</sup> Further work is needed given the large numbers of Africans living with HIV and the high prevalence of depression in this population.<sup>28-31</sup>"

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**Competing Interests:** No competing interests were disclosed.