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RESEARCH ARTICLE

The effect of sertraline on depression and associations with persistent depression in survivors of HIV-related cryptococcal meningitis [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Depression is a risk factor for worse outcomes in persons living with HIV/AIDS and has a prevalence more than three times as high as in the general population. Despite this, there are few randomized studies of antidepressants in HIV-infected Africans.
Methods: We enrolled 460 HIV-infected Africans with cryptococcal meningitis into a randomized clinical trial of adjunctive sertraline vs placebo (2015-2017). We defined depression using depression using a Center for Epidemiologic Studies Depression Scale (CES-D) score of >15, and 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),

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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 who had 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

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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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Introduction

Chronic illnesses, particularly when advanced, are associated with deterioration in mental health[1]. More than 300 million individuals suffer from major depressive disorder worldwide[2]. In persons living with HIV/AIDS, the prevalence of depression is up to three times more common than in the general population[3,4], making depression one of the most common neuropsychiatric complications in these individuals[5]. The under-diagnosis of major depression in people with HIV[6] undoubtedly contributes negatively to individuals' overall well-being. People diagnosed with depression and HIV-infection often have poorer clinical and HIV outcomes than those diagnosed with HIV infection without depression[7,8]. 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[9]. However, there is surprisingly little data on the efficacy of depression therapies in individuals with HIV[10–12].

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)[13]. 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 who had been in 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[13]. 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[13]. 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. We defined depression as a CES-D score of >15 on a 0 to 60-point total scale[14,15]. Mulago National Referral Hospital (MREC 429) and the University of Minnesota Institutional Review Boards (1304M31361) approved the protocol. Written informed consent was provided by all participants or their surrogates.

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 ≥26[16]. 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[17]. 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[18]. We calculated odds ratios to assess 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[13]. The median CD4 count was 15 cells/mcL, and 41% of the enrolled subjects were women. Baseline characteristics are shown in Table 1[19]. There were no significant differences at baseline by randomized groups. Overall, 273 (59%) survived more than a month, and 234 (51%) survived through more than 3 months.

Differences between those screened and unscreened for depression

We selected those who survived to 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 to one month 174 (64%) had depression screening performed at one month and 169 (72%) at three months.

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*
Demographics			
Age, years	35 (30-41)	35 (29-40)	0.234
Women	37.7%	97 (42.4%)	0.304
CD4 cell count, cells/mm^3	13 (6-41)	17 (7-47)	0.362
Receiving ART	48.1%	48.9%	0.854
Baseline CSF Analysis			
Opening pressure, mm H_2O	270 (180-410)	248 (170-380)	0.172
Opening pressure >200 mm H_2O	68.5%	60.7%	0.100
Cryptococcal culture, log_{10} 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^3	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^{nd} lumbar puncture opening pressure, mmH_2O**	260 (140-400)	260 (180-400)	0.859
Day 14 CSF opening pressure, mmH_2O	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^{nd} LP at day 2–5 and N=199.

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

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_2O (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 related to illness.

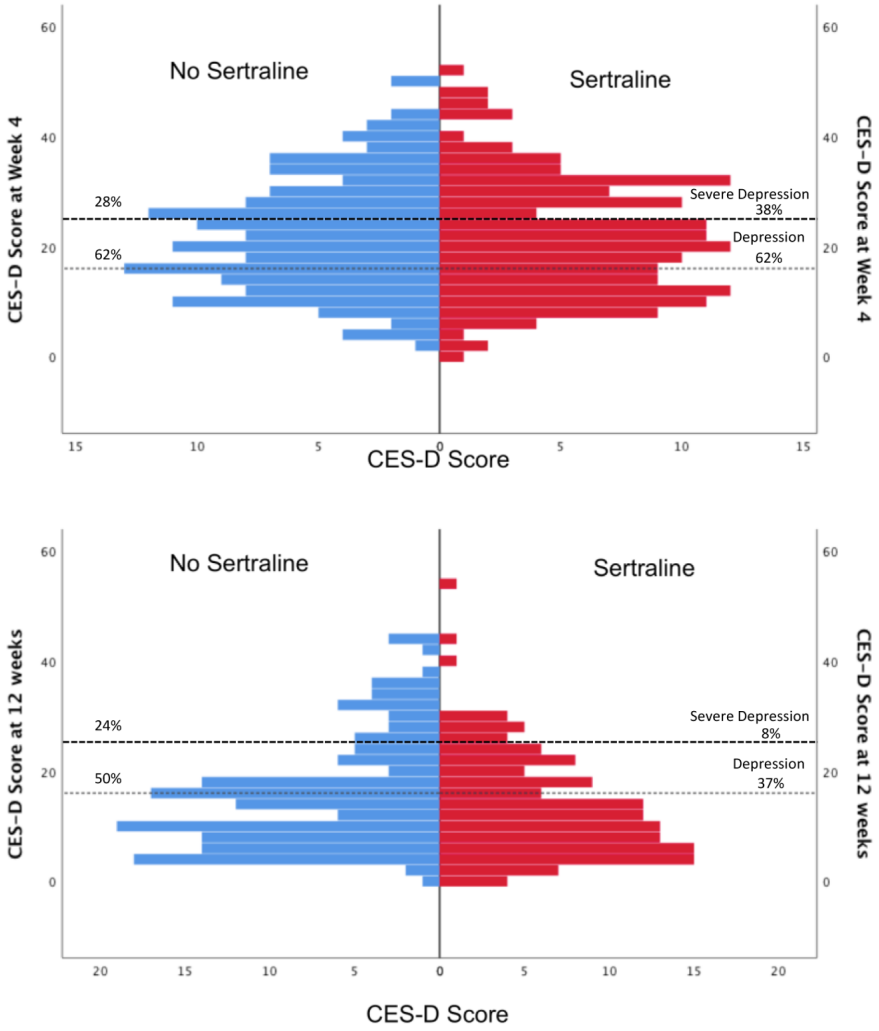
Impact of sertraline on depression

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 compared to those not on sertraline (p=0.030).

In Figure 1, a population pyramid is displayed comparing 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. 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 when compared with those that received 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 ≥16) at one-month post meningitis diagnosis,



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%	***0.006***	***0.335 (0.130-0.865)***

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.

which is the time of entering into outpatient HIV care. We also evaluated the baseline (one month) to endpoint (three month) 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[19]). 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). 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%,

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 ≥16 (N=74) Median (IQR)	No Depression CES-D <16 (N=95) Median (IQR)	P-value*
CES-D Score at three months	23 (18-30)	8 (4-11)	----
Demographics			
Age, years	34.5 (29.0-40.0)	35.0 (29.0-38.0)	0.313
Women	40.5%	28.4%	*0.098*
Clinical characteristics			
Glasgow Coma Scale Score <15	44.6%	31.6%	*0.083*
CD4 cell count, cells/mm^3	16 (7-51)	19 (8-52)	0.996
Receiving ART	40.5%	49.5%	0.247
Baseline CSF Analysis			
Opening pressure, mm H_2O	265 (180-370)	260 (200-340)	0.919
Opening pressure >200 mm H_2O	64.5%	73.3%	*0.254*
Cryptococcal culture, log_{10} 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 ≥5 cells/mm^3	45.7%	44.2%	0.848
CSF protein, mg/dL	50.0 (20-141.5)	49.5 (20.8-120.0)	0.638
Follow-up CSF Analysis			
Day 14 CSF Opening pressure >200	43.2%	51.9%	0.393
Depression at One Month			
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

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 did significantly lower 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, as well as 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 participants in this study 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 who were from areas outside of Kampala, as well as those who had 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. 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.

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[20], a case series of HIV-negative individuals with cryptococcal meningitis[21], and two case reports where HIV-statuses were not revealed[22,23]. 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.

There is surprisingly little data about the use of antidepressants in Africans living with HIV. In South Africa, Hoare *et al.* conducted a randomized controlled trial of escitalopram in those with HIV-associated depression[24]. 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[10]. Further work is therefore desperately needed given the large numbers of Africans living with HIV and the high prevalence of depression in this population[25–28].

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 trial 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 those with depression at baseline and significantly associated with severe depression in all-comers. Larger randomized, controlled trials are needed examining 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[19]

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).

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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^3, 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 data 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[1]).

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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.