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RESEARCH ARTICLE

# REVISED Neurocognitive outcomes of tuberculous meningitis in a primarily HIV-positive Ugandan cohort [version 2; peer review: 1 approved, 2 approved with reservations]

Previously titled: 'Neurocognitive outcomes of HIV associated tuberculous meningitis'

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## Abstract

**Background:** The toll of tuberculous meningitis (TBM) in both mortality and disability is considerable, but advancements in rehabilitation have the potential to improve the functional abilities and the quality of survivors' lives. However, the typical phenotype of neurocognitive impairment in TBM survivors remains unstudied in HIV-predominant populations in sub-Saharan Africa.
**Methods:** We tested 36 survivors of TBM in Uganda with a comprehensive battery of neurocognitive assessments at 8 and 24 weeks after diagnosis, and compared results to a representative cohort of HIV-uninfected Ugandans.
**Results:** While participants had a broad range of impairments at eight weeks, there was marked improvement by 24 weeks, when a phenotype of impairment including deficits in motor functioning, verbal learning and memory, processing speed, and executive function emerged. These deficits were present despite good clinician-rated functional status. The majority (23/27, 85%) had evidence of moderate to severe depression at week 8, and at week 24 (18/24,

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75%).
**Conclusion:** These findings highlight the need for more comprehensive neurocognitive assessment in the survivors of TBM, and further investment in and study of rehabilitation, including management of depression, to improve long-term outcomes in this population.

**Keywords**
Tuberculous Meningitis, HIV, neurocognitive, functional, psychiatric, depression

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**REVISED** **Amendments from Version 1**

Adjustments were made to the text based on recommendations from reviewers. These include additional limitations of the study regarding language of assessment administration, practice effects, and the inability to draw conclusions on the impact of trial treatments and HIV status. Two new tables and associated text passages were added to provide data on the HIV-negative control group (Table 2), and to detail the neurocognitive testing results when severely impaired participants were included and excluded (Table 5). The title was modified to better reflect that the population in the study was primarily HIV-positive.

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

## Introduction

Tuberculous meningitis (TBM) continues to incur unacceptably high mortality, especially in people living with HIV, in whom it can exceed 50%[1,2]. The persistence of neurologic sequelae in those who survive has been long-recognized, and can include major neurologic deficits such as hemiplegia and blindness, as well as more subtle cognitive changes such as memory or psychiatric problems[3,4]. The various neurologic sequelae have been reported to affect a third to a half of survivors in some series[1,2]. These long-term neurological complications are attributed to hydrocephalus[5], decreased grey matter volume[6], and stroke, which may occur in as many as 57% of patients[7,8].

The most commonly employed assessments for long-term morbidity in TBM are the modified Rankin Scale or Barthel Index, with recent meta-analyses reporting some physical disability in 32% of TBM survivors, using these tools[1]. While the importance of severe disability is recognized, and often an endpoint in TBM clinical trials[9], these broad measures can miss the more subtle neurocognitive changes in TBM patients that can still impact overall wellbeing and economic output[10]. Two Indian cohort studies used the Mini Mental Status Exam and found cognitive impairment in over half of survivors at six months and one year after TBM diagnosis[11,12]. Comprehensive neuropsychological testing using the Wechsler Adult Intelligence Scale in 17 TBM patients in Taiwan showed impairment in multiple domains including working memory and verbal comprehension[6]. However, these studies in HIV-negative populations may not be representative of TB-HIV coinfection, as HIV, both independently and in conjunction with TB, contributes to neurocognitive impairment[13,14]; yet, TBM in HIV-infected persons is less inflammatory[15]. Given recent findings of variability in reliability of cognitive assessments across different regional and cultural settings[16], it is essential that neurocognitive assessments are modified and standardized to local norms, as has been successfully applied in past studies of neurocognitive outcomes after cryptococcal meningitis[17,18]. Comprehensive neuropsychological testing has never been reported after TBM in a primarily HIV-positive population or in sub-Saharan Africa. Furthermore, despite evidence of increased risk of mental illness in childhood survivors of TBM[19], the burden of depression in adult survivors of TBM is unknown.

Given the prevalence of disability in TBM survivors, further understanding of rehabilitation options is necessary. In 2017, the World Health Organization (WHO) identified rehabilitation as an increasing unmet need to address disability in low and middle income countries, and called for strengthening of these systems[20]. In Uganda, availability of physiotherapy remains limited, and is often restricted to those with higher socioeconomic status and education[21]. Neurorehabilitation has emerged as a specialized form of rehabilitation incorporating physiotherapy as well as occupational, speech, and psychiatric therapy, to target the potential for brain recovery in neurological diseases such as stroke and multiple sclerosis[22]. Groups in India and West Africa have investigated telemedicine strategies for the rehabilitation of survivors of stroke, TBM, and other neurologic illnesses to overcome implementation barriers that exist in resource-limited settings[23,24].

To better target neurorehabilitation resources, a clearer phenotype of the neurocognitive and functional impairment in TBM is necessary. In this nested prospective cohort study, we assessed detailed neurocognitive function, alongside depression and functional status, in Ugandan clinical trial participants who survived TB meningitis. To describe the cognitive deficits associated with TBM and their improvement over the first 6 months of recovery, tests were repeated at 8 and 24 weeks, and compared with a representative healthy control group.

## Methods

### Population and setting

Patients were enrolled in this prospective cohort from within the "*High dose oral and intravenous rifampicin for improved survival from adult tuberculous meningitis*" (RIFT) study, a phase 2 open-label randomized trial (ISRCTN42218549)[25]. Patients were enrolled in the parent trial between January 14 and December 17, 2019, at Kiruddu National Referral Hospital in Kampala, Uganda and Mbarara Regional Referral Hospital in Mbarara, Uganda, based on detection of TB in the cerebrospinal fluid (CSF) by Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA)[26], or presentation compatible with TBM (CSF:plasma glucose ratio <50% or CSF glucose <65 mg/dL), coupled with TBM treatment planned. Exclusion criteria and study drug administration details are provided in the published trial protocol[27]. We recorded baseline clinical data, CSF results, and demographics at initial presentation. Adjunctive corticosteroids were administered to all patients and antiretroviral therapy (ART)-naïve individuals initiated ART after completion of the intensive phase of TB treatment (week 8), in accordance with Ugandan guidelines (tenofovir/lamivudine/dolutegravir as first-line). HIV-positive participants also received cotrimoxazole prophylaxis.

We enrolled participants into this sub-study assessing neurocognitive and functional outcomes from the Kampala site eight weeks after their enrollment in the parent trial.

We included those who survived the initial hospitalization and presented for their week eight post-randomization clinic follow-up visit. We excluded patients whose meningitis was later confirmed to be due to a non-TB etiology.

### Procedures

At week 8 and 24 visits, patients' clinical status was recorded, as was their modified Rankin score and Karnofsky performance score, clinician-determined functional status measures. They were screened for depression using the patient health questionnaire (PHQ)-9 instrument, which ranges from 1 to 27 and has been validated in multiple countries in sub-Saharan Africa with a cutoff of 10 for moderate or severe depression[28,29]. We used a secondary cutoff of 15 to account for possible overlap in physical symptoms with TBM illness. As part of the visit, participants received a standardized battery of neurocognitive tests in either English or Luganda performed by a trained study nurse. The battery of tests evaluates ten neuropsychological and motor domains, and has been validated in sub-Saharan African populations and performed in Uganda on survivors of cryptococcal disease[17,30]. These tests have become the standard for use in Uganda as past studies have validated the Luganda translations[31], and shown minimal difference in score based on English or Luganda administration[32]. The WHO-University of California-Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT) assesses verbal learning and memory[33], Digit Span Forward and Backward assesses attention and working memory[34], Semantic Verbal Fluency assesses language fluency[35], Timed Gait assesses gross motor function[36], Grooved Pegboard (average of both hands) assesses fine motor function[37], Finger Tapping (of the dominant hand) assesses motor speed[38], Symbol Digit Modality assesses processing speed and concentration[39], Color Trails 1 assesses processing speed and attention, and Color Trails 2 assesses executive function[40], (Table 1).

### Statistical analyses

Raw scores on each test were standardized to duration of education (<7 years, 7 to 12 years, and >12 years) and age (greater or less than 30 years), matched to HIV-negative Ugandan controls (data collected as part of a prior neurocognitive study[32,41] and summary statistics presented in Table 2) to create education- and age-adjusted Z-scores. To generate a global measure of neurocognitive function across all domains, a quantitative neurocognitive performance Z-score (QNPZ-8) was calculated as the mean of eight individual Z-scores: Symbol Digit, WHO-UCLA AVLT immediate and delayed recall, Verbal Fluency, Color trails 1 and 2, Finger Tapping, and Grooved Pegboard. We defined neurocognitive impairment as one standard deviation below the HIV-negative reference mean

**Table 1. Neuropsychological test battery and neurocognitive domains evaluated.**

| Test | Test Description | Cognitive Domains |
|---|---|---|
| WHO-UCLA AVLT-Total* | Subjects are asked to recall a list of words. The test is similar to the Rey Auditory Verbal Learning test, however words have been selected to be recognizable to a variety of cultures | Verbal learning |
| WHO-UCLA AVLT-Delayed Recall* | Similar to WHO-UCLA AVLT, but subjects are asked to recall the same list of words in a delayed recall phase | Verbal memory |
| Digit Span Forward and Backward | Subjects are given a series of digits of increasing length and are asked to repeat them in forward or backward order | Attention, Working memory |
| Semantic Verbal Fluency | Subjects are given 60 seconds to produce as many words as possible within a specific category such as 'animals' | Language fluency (Verbal) |
| Symbol Digit Modality | Subjects are asked to match geometric figures to numbers as quickly as possible over 90 seconds using a visual reference. | Speed of information processing, Concentration |
| Color Trails 1 | Subjects connect encircled numbers scattered on a page in sequence during a set amount of time. This test is similar to the Trail Making Test but has been formulated to minimize cultural bias by not using any letters or written instructions | Speed of information processing, Attention |
| Color Trails 2 | Similar to The Color Trails 1 but each number is printed in two different colors, and subjects are asked to maintain the numerical sequence while alternating colors | Executive function |
| Timed Gait | The time for subjects to walk out and back 10 meters is recorded | Gross motor |
| Grooved Pegboard | Subjects are timed while placing pegs which each have a key along one side in holes in various orientations in a pegboard with either their dominant or non-dominant hand | Fine motor |
| Finger tapping | Subjects tap as rapidly as possible using the index finger on a specially adapted tapper for five 10-second trials | Motor speed |

WHO-ULCA AVLT = World Health Organization-University of California-Los Angeles Auditory Verbal Learning test

(corresponding to a Z-score of -1) and severe impairment as two standard deviations (Z-score < -2). Participants were permitted to skip tests if they started but were unable to complete it due to visual difficulties, fatigue, or physical limitations. Skipped tests were assigned Z-scores equal to the mean of the TBM cohort minus two standard deviations. All analyses were run on STATA version 15 (StataCorp, College Station, TX).

### Ethical considerations

Written informed consent was obtained from participants or their caregiver. The parent trial and this sub-study were approved by the Research Ethics Committees of LSHTM, UK, Mulago Hospital, Uganda National Council of Science and Technology, and Uganda National Drug Authority. An independent data safety committee reviewed accruing data from the parent trial.

**Table 2. Demographic data on HIV-negative control cohort (n=100).**

| Characteristics at Enrollment | |
|---|---|
| Age, years | 31 (27-35) |
| Women | 53 (53%) |
| Education <7 years | 18 (18%) |
| 7–12 years | 60 (60%) |
| >12 years | 22 (22%) |

**Values are medians with interquartile range (IQR) or N (%).**

## Results

### Cohort

Of 56 patients enrolled in the parent trial at Kampala, 37 survived and remained at eight weeks follow-up to be considered for enrollment in this study (Figure 1). The 19 not considered for enrollment either did not survive to week 8 (n=14), were withdrawn from the parent trial during the initial hospitalization (n=3), or were unable to present to their week 8 visit and later died (n=2). We enrolled 36 patients into the neurocognitive study after excluding one who had an alternate etiology of meningitis. Of the 36, 28 were reassessed at week 24 (n=6 died, n=2 declined assessment at week 24).

Demographics and clinical data from the initial hospitalization are presented in Table 3. The cohort was relatively young (median age 35). Overall, 42% (15/36) had less than 7 years of education, 39% (n=14) had seven to 12 years of education, and 19% (n=8) had more than 12 years of education. Compared to the HIV-negative control group (Table 2), there was a higher proportion with fewer years of education, but age and gender were similar. Overall, 94% (34/36) were HIV-positive, and 44% (16/36) had microbiological-confirmed TBM. Due to low numbers in each experimental treatment group (standard of

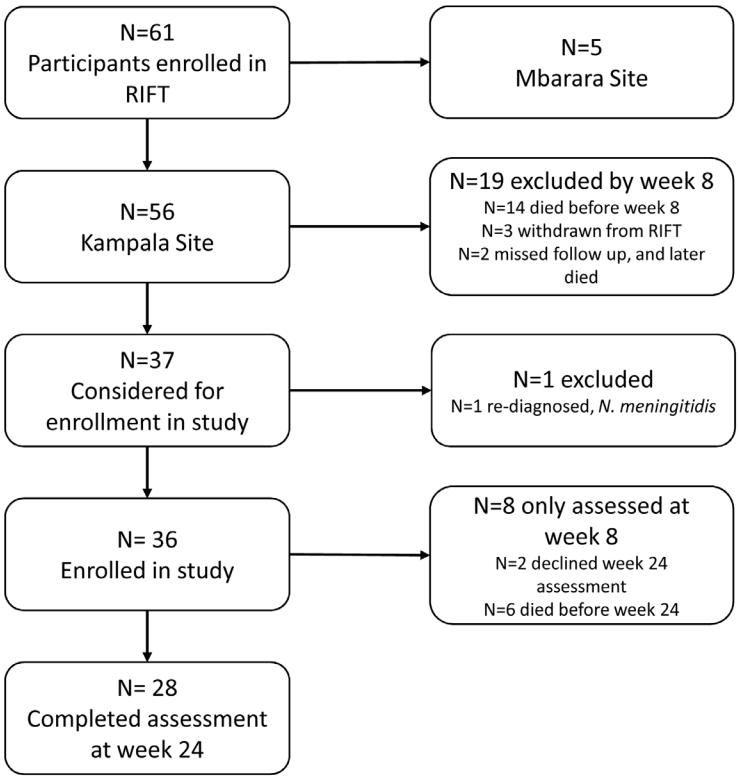


**Figure 1. Enrollment in this nested sub-study from the parent randomized RIFT trial.**

**Table 3. Baseline results in persons with TBM.**

| Characteristics at Diagnosis | |
|---|---|
| Age, years | 35 (29-37) |
| Women | 18 (50%) |
| Education <7 years<br>7–12 years<br>>12 years | 15 (42%)<br>14 (39%)<br>7 (19%) |
| HIV-positive | 34 (94%) |
| Receiving ART (of HIV-positive) | 12 (35%) |
| CD4 count, cells/μL | 111 (43-272) |
| CD4 count <200 cells/μL | 19 (61%) |
| Microbiologically-confirmed TBM | 16 (44%) |
| Trial Arm: Standard of Care<br>High dose oral rifampin<br>High dose IV rifampin | 15 (42%)<br>10 (28%)<br>11 (31%) |
| TBM severity: MRC grade 1<br>2<br>3 | 4 (11%),<br>27 (75%),<br>5 (14%) |
| Glasgow Coma Scale score | 14 (12-14) |
| CSF White Blood Cell Count, cells/μL | 35 (<5-125) |
| CSF Protein, mg/dL | 128 (94-177) |
| CSF Glucose, mg/dL | 41 (21-68) |
| Serum Sodium, mEq/L | 130 (126-136) |

Values are medians with interquartile range (IQR) or N (%).

ART: antiretroviral therapy, TBM: Tuberculous meningitis, MRC: medical research council grade, CSF: cerebrospinal fluid.

care n=15, high dose oral rifampin n=10, high dose intravenous rifampin n=11), neurocognitive data is described for the cohort as a whole rather than by randomized treatment group from the parent trial; data from the parent trial suggests no significant difference in function outcomes or mortality between the treatment groups[25].

### Week 8 neurocognitive assessment

At eight weeks, 11 patients had at least moderate disability with a modified Rankin Scale score greater than or equal to 3 (median cohort score = 2, IQR 1-3), and 75% (27/36) of patients had Karnofsky scores <80, indicating inability to carry on normal activity (Table 4).

At week 8, 86% (31/36) of patients had impaired cognitive function (QNPZ-8 lower than -1), and 53% (19/36) had severe impairment (QNPZ-8 lower than -2). The mean QNPZ-8 score was -2.51 (standard deviation (±SD) ±1.43) representing 2.51 standard deviations (i.e. Z-score) below the control group mean for HIV-negative Ugandans, adjusted for age and education. At eight weeks, impairment was nonspecific as all

**Table 4. Week 8 and 24 neurocognitive and functional outcomes in persons with tuberculosis meningitis.**

| | Week 8 | Week 24 |
|---|---|---|
| modified Rankin Scale > 2 | 11 (31%) | 3 (10%) |
| Karnofsky Functional Status Score < 80 | 27 (75%) | 6 (21%) |
| PHQ-9 Depression Score ≥ 10 | 23 (85%) | 18 (75%) |
| PHQ-9 Depression Score ≥ 15 | 19 (70%) | 14 (58%) |
| QNPZ-8 Neurocognitive <-1 Z-score | 31 (86%) | 17 (61%) |
| QNPZ-8 Neurocognitive <-2 Z-score | 19 (53%) | 7 (25%) |

Abbreviations: PHQ-9: patient health questionnaire 9

component assessments of the QNPZ-8 demonstrated cognitive impairment (Z-score < -1) on the cohort-level. Specific domains with severe impairment included executive function (color trails 2 assessment: -4.93, SD±3.20); verbal learning (AVLT-Total: - 2.93, SD±1.66); verbal memory (AVLT-Recall: -3.21, SD±2.66); and speed of information processing (color trails 1 assessment: -2.20, SD±2.31) (Figure 2). While gross motor performance does not contribute to QNPZ-8, gross motor performance as assessed by timed gait was severely impaired, with a mean Z-score of -7.89 (SD±3.40).

### Week 24 neurocognitive assessment

At week 24, three patients had at least moderate disability (median modified Rankin = 0, IQR 0-1), and 21% (6/28) of patients had a Karnofsky score <80 (Table 4).

At week 24, 61% (17/28) of patients had impaired cognitive function, and 25% (7/28) had severe impairment (Figure 3). Mean QNPZ-8 at 24 weeks was -1.62 (SD ±1.29). Amongst the 28 patients tested at both time points, QNPZ-8 improved from a mean of -2.39 (SD ±1.52) to -1.62 (SD ±1.29). The most improved domains over these 16 weeks were fine motor (grooved pegboard, Z-score difference = 1.15) which improved to the mean of the HIV-negative Ugandan control group, and executive function (color trails 2 assessment, Z-score difference 1.32) which remained severely impaired (Figure 2). Other domains which remained impaired were processing speed (color trails 1: -1.32 (SD ±1.66)) (symbol digit modality: -1.33 (SD ±1.21)), verbal learning (AVLT-total: -1.86 (SD ±1.65)), verbal memory (AVLT Recall: -2.16 (SD ±2.01)), and motor speed (finger tapping: -1.58 (SD ±1.20)). Color trails 1 and symbol digit modality also assess concentration and attention; however, these domains were judged unimpaired based on relatively normal results on tests of concentration and attention which do not test processing speed: digit span forward and backward (-0.76 SD ±2.1; -0.14 SD ±2.6 respectively). Timed gait remained severely impaired: mean Z-score was -5.11 (SD ±3.69).

Of note, seven patients at eight weeks, and two patients at 24 weeks were too ill to complete any test and therefore all scores including QNPZ-8 are imputed 2 standard deviations

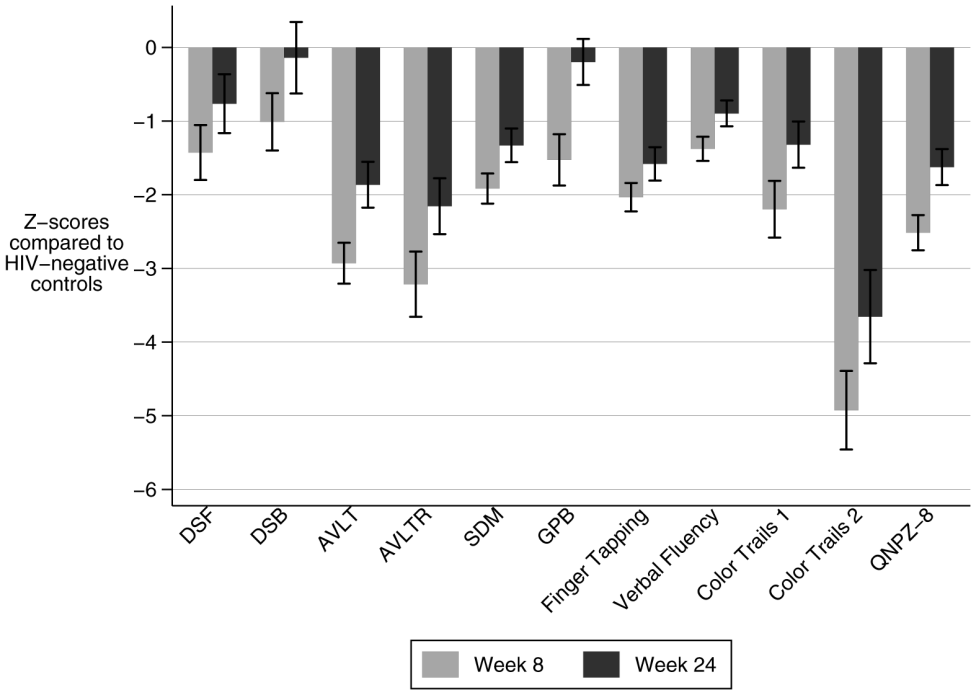


**Figure 2. Impairment in neurocognitive domains at eight and 24 weeks in survivors of TBM.** Mean cohort Z-scores in each neurocognitive assessment and the summary score (QNPZ-8) at both time points show improvement in most domains. A Z-score <-1 signifies impairment, and a Z-score <-2 signifies severe impairment. Error bars represent standard error. DSF: Digit Span Forward, DSB: Digit Span Backward, AVLT: WHO-UCLA Audio Verbal Learning Test Total, AVLTR: WHO-UCLA Audio Verbal Learning Test Recall, SDM: Symbol Digit Modality, GPB: grooved pegboard, QNPZ-8: Quantitative neurologic performance on eight modalities.

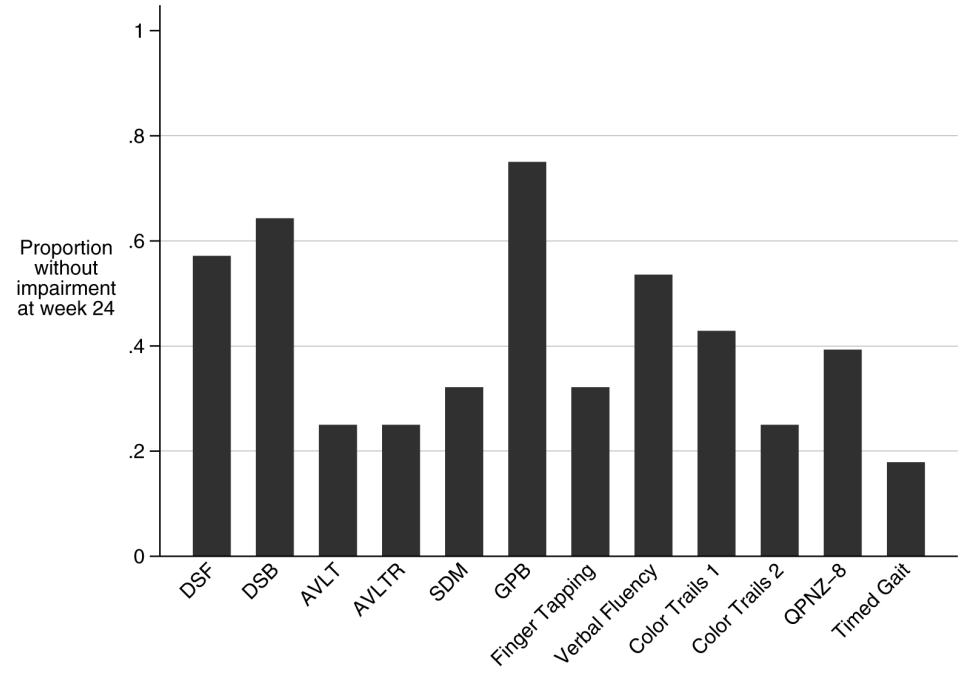


**Figure 3. Proportions of the cohort that are no longer impaired in each assessment at week 24.** Bars approaching 1 signify few participants with impairment in that domain. Majorities of the cohort have impairment in AVLT, AVLTR, SDM, Finger tapping, Color Trails 1, Color Trails 2, Timed Gait, and the summary score (QNPZ-8). Impairment on any given assessment is defined as a Z-score <-1. DSF: Digit Span Forward, DSB: Digit Span Backward, AVLT: WHO-UCLA Audio Verbal Learning Test Total, AVLTR: WHO-UCLA Audio Verbal Learning Test Recall, SDM: Symbol Digit Modality, GPB: grooved pegboard, QNPZ-8: Quantitative neurologic performance on 8 modalities.

below the cohort mean. In a parallel analysis excluding these patients (Table 5), mean scores were slightly improved but relative differences between domains were similar in both populations (Timed Gait, Color trails 1, color trails 2, AVLT, AVLTR were most impaired; Digit span forward, digit span backward, verbal fluency, grooved pegboard were least impaired).

### Depression screening

Moderate and severe depression, as defined by a PHQ-9 score ≥10 was present in a majority of the cohort (23/27 (85%) able to complete the questionnaire) at week 8. At week 24, rates of moderate and severe depression were somewhat lower (75%; 18/24), but still constituted a large majority of the cohort. Even with a higher cutoff (≥15), the majority screened positive for depression at both time points (Table 4). Among the 21 who completed the questionnaire at both time points, moderate and severe depression was present in 17 (81%) at week 8, and 15 (71%) at week 24.

## Discussion

In this prospective study of 36 survivors of TBM in Uganda, we have reaffirmed the high degree of early functional disability present, demonstrated neurocognitive and functional improvement between two and six months, and described a phenotype of neurocognitive impairment predominantly in executive functioning, information processing speed, and verbal learning and memory. This phenotype is less apparent at eight weeks, when patients are often still recovering from their acute illness and are broadly impaired, but by 24 weeks becomes clear as some neurocognitive domains approach control group norms while others remained impaired. Notably, at this time many patients were judged as clinically well and without significant disability (based on the modified Rankin Scale) by the study doctor, but there remained significant neurocognitive deficits that were identified on comprehensive neurocognitive testing. Longer follow-up is necessary to determine the durability of this impairment, and whether longer-term recovery is likely.

Many of the deficits identified were motor-related, including gross motor (timed gait), fine motor (grooved pegboard), and motor speed (finger tapping). Of the more explicitly cognitive domains, verbal learning and memory, processing speed, and executive function were especially affected. The deficits described mirror many of those found in a prior Taiwanese study (which did not test motor domains), where TBM survivors had significant deficits in processing speed (digit symbol), verbal comprehension (similarities), working memory (letter-number sequencing), and additionally, perceptual organization (block design, matrix reasoning)[6]. While this suggests potential generalizability of TBM neurocognitive outcomes between HIV-positive and HIV-negative populations, further study is necessary.

Reflecting the epidemiology of TBM in Uganda[42], a majority of the cohort was HIV-positive and among those, a majority had a baseline CD4 T cell count <200 cells/μL, putting them at significant risk of HIV-associated dementia[43]. Dissecting the neurocognitive impacts of HIV infection and TBM is inherently difficult, and current definitions of HIV-associated dementia exclude patients with central nervous system opportunistic infections like TBM[44]. The typical profile of neurocognitive impairment in HIV-associated dementia includes deficits in verbal learning and memory, executive functioning, attention,

**Table 5. Mean Z-score with standard deviation on each neurocognitive test at week 8 and 24 in the full study cohort and in only participants who attempted neurocognitive assessment.**

| Neurocognitive Test | All Participants Week 8 (n=36) | Participants Who Attempted Week 8 (n=29) | All Participants Week 24 (n=28) | Participants Who Attempted Week 24 (n=26) |
|---|---|---|---|---|
| Digit Span Forward | -1.43 ± 2.24 | -0.95 ± 2.24 | -0.76 ± 2.11 | -0.56 ± 2.09 |
| Digit Span Backward | -1.01 ± 2.33 | -0.40 ± 2.18 | -0.14 ± 2.57 | 0.13 ± 2.51 |
| AVLT | -2.93 ± 1.66 | -2.41 ± 1.35 | -1.86 ± 1.65 | -1.63 ± 1.46 |
| AVLT Recall | -3.21 ± 2.66 | -2.56 ± 1.94 | -2.16 ± 2.00 | -1.83 ± 1.42 |
| Symbol Digit Modality | -1.92 ± 1.23 | -1.86 ± 1.36 | -1.33 ± 1.21 | -1.27 ± 1.26 |
| Grooved pegboard | -1.53 ± 2.09 | -1.22 ± 2.23 | -0.20 ± 1.49 | 0.00 ± 1.58 |
| Finger Tapping | -2.03 ± 1.16 | -1.73 ± 1.09 | -1.58 ± 1.20 | -1.45 ± 1.17 |
| Verbal Fluency | -1.37 ± 0.99 | -1.09 ± 0.88 | -0.90 ± 0.93 | -0.77 ± 0.85 |
| Color Trails 1 | -2.20 ± 2.31 | -2.24 ± 2.57 | -1.32 ± 1.66 | -1.27 ± 1.74 |
| Color Trails 2 | -4.93 ± 3.20 | -4.99 ± 3.54 | -3.65 ± 3.35 | -3.58 ± 3.53 |
| Timed Gait | -7.89 ± 3.41 | -7.38 ± 3.61 | -5.11 ± 3.69 | -4.73 ± 3.63 |
| QNPZ-8 | -2.51 ± 1.43 | -2.26 ± 1.49 | -1.62 ± 1.29 | -1.47 ± 1.24 |

Abbreviations: AVLT: WHO-UCLA Auditory Verbal Learning test (See Table 1)

and processing speed[32,45]. The deficits we described in TBM survivors in memory, executive functioning, and processing speed overlap this profile, although the additional deficits in gross motor domains, and relatively good performance in tests of attention not relying on speed, are notable. When the same battery of neurocognitive tests was administered to an HIV-positive cohort in Uganda[32], participants were impaired in verbal learning, gross motor, and executive function, but to a lesser degree than in this TBM cohort at 24 weeks (comparable Z-scores presented[17]). This suggests neurocognitive impairment after TBM beyond what would be expected from HIV alone. ART improves symptoms of HIV-associated dementia[30], and 24 week testing on TBM survivors in our study (16 weeks after ART initiation) showed significant but far from complete improvement from baseline. Longer follow-up and evidence of immune recovery is necessary to better understand the contribution of HIV to the neurocognitive impairment after TBM.

We found a high prevalence of depression in survivors of TBM at both eight and 24 weeks. This is consistent with findings of high rates of depression in South African children with TBM[19]. Interestingly, the rates of depression in this study are higher than in adult survivors of cryptococcal meningitis in Uganda (73% at one month in a 2010–2013 cohort, 62% in a 2015–2017 cohort)[17,46]. While there has been little study of the relationship between TBM and depression, the pathophysiology and treatment of TBM in our cohort involves HIV infection, inflammation, neurologic injury, and glucocorticoids, all of which are also associated with depression[47–51]. IL-6, known to play an important role in depression[52–54], including inhibiting the serotonin pathway, is significantly associated with the severity of TBM[55]. Cognitive impairment is a known symptom of depression[56], so some of the cognitive impairment seen in the cohort could be attributable to depression. As prior psychiatric illness was not assessed, we cannot determine whether premorbid depression may have also contributed to risk of advanced HIV and TBM. Given the association between depression and HIV-induced immunosuppression[14], it is notable that unlike the significant improvement in depression reported after ART initiation in survivors of cryptococcal meningitis[17,57], high rates of depression persisted in our cohort at six months, well after ART was initiated. Immunologic differences in the response to cryptococcal meningitis and TBM[55], known to be important in the development and persistence of depression[58,59], may partly explain this disparity. Differences between TBM and cryptococcal meningitis disease severity could further explain the difference in depressive symptoms, with TBM having higher rates of altered mental status while hospitalized[46,60–62], strokes[7,8,63], and persistent neurologic deficits. A comprehensive treatment of depression is essential to improve outcomes in TBM, and should be incorporated into follow-up and rehabilitation protocols.

The improvement in both motor and cognitive domains over six months is remarkable even without formal rehabilitation, but further recovery potential remains unknown. Given the predominance of motor impairment, physiotherapy could provide significant benefits, and deserves further study. More specialized rehabilitation practices might show benefit in the recovery from deficits in processing speed, executive function, and memory. Rehabilitation protocols designed for stroke survivors, which are the most available worldwide[22,24], could be effective for TBM given that there is also a high prevalence of motor deficits, depression, and cognitive deficits (especially executive function and processing speed), although the exact phenotype of cognitive deficits differs depending on stroke location[64,65]. This population (median age 35 years) are in the most economically active period of life and thus rehabilitation may prove to be cost-effective. Further investment in local physiotherapy is essential in sub-Saharan Africa, but increasing experience with telemedicine provides an alternate method of care delivery[23,24]. Novel approaches, including brain-training video games, might be applicable for recovery from TBM as they have shown promise in improving working memory and processing speed in other populations[66,67].

Strengths of this study include standardization of results to a locally representative cohort and detailed neurocognitive profiling at two time-points. Specifically, the neurocognitive instrument used has been validated in both languages of administration, although a limitation is that little detail is available on the specifics of the translation process between English and Luganda and whether it met established guidelines. Other limitations include the small cohort size and lack of follow up beyond 6 months. The study was not powered to assess the impact of the trial treatment on neurocognitive outcomes, which may limit generalization to populations not receiving these non-standard TB therapies. However, the parent trial found no difference in mortality, functional status, or time to resolution of coma, although it too was not powered to assess these outcomes[25]. There were also too few HIV-negative participants to assess for differences in neurocognitive outcomes between HIV-positive and negative participants. The control group had only 100 participants, limiting the ability to assume true population norms. The control group was more educated, but analysis of education-adjusted scores intended to minimize any impact. Larger studies will be necessary to investigate baseline risk factors for poor neurocognitive outcome. The same assessment was given to participants at 8 and 24 weeks in order to track neurocognitive improvement; however, this could incur an element of practice effects that explains some of the improvement in scores. We intended to mediate these effects with a 16 week gap between successive testing sessions, but since the control group did not take the assessment multiple times, it is possible we did not completely adjust for these effects.

Eight weeks from diagnosis may be too early to meaningfully determine neurocognitive outcomes in TBM survivors as a substantial proportion of participants (19%) at that time were remained too acutely ill to attempt any neurocognitive testing. While those participants were included in order to fairly represent the degree of impairment still present at 8 weeks and allow for comparison to the literature, their blanket impairment may not represent the phenotype of impairment in survivors who are further along in their recovery. Notably, by

12 weeks, only 7% of participants were too ill to participate, so the phenotype at this time point may be more representative.

Comprehensive neurocognitive testing of TBM survivors in sub-Saharan Africa is feasible. There is significant neurocognitive recovery between 2 and 6 months, but significant deficits remain in motor domains, as well as processing speed, verbal learning, and executive function. These findings highlight the need for neurorehabilitation and management of depression in TBM survivors.

## Data availability

### Underlying data

Repository name: Data Compass, https://doi.org/10.17037/DATA.00002372[68]

This project contains the following underlying data:

- Individual baseline results
- Individual clinical statuses at weeks 8 and 24
- Modified Rankin, Karnofsky performance,and PHQ-9 scores
- Individual raw scores for each test in the battery of neurocognitive tests
- Individual Z-scores on the neurocognitive tests

Data are available under the terms of the Data Sharing Agreement. Due to ethical considerations surrounding the sensitivity of the data in a vulnerable population, study consents limited the access to underlying data from this study. However, controlled access to the data posted in the above repository is permitted after signing of the agreement and IRB approval. Readers interested in the data can learn more by completing the application form on the Data Compass repository, or by contacting the LSHTM Research Data Management Service at researchdatamanagement@lshtm.ac.uk with the dataset DOI.

### Acknowledgements

We thank Dr. Ned Sacktor for his pioneering work in neurocognitive assessments in Africa.

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http://www.doi.org/10.17037/DATA.00002372

# Open Peer Review

## Current Peer Review Status: ✔ ? ?

**Version 2**

Reviewer Report 28 July 2022

https://doi.org/10.21956/wellcomeopenres.19643.r51357

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**Pablo F. Belaunzarán-Zamudio**
Division of AIDS, National Institutes of Allergy and Infectious Diseases, Mexico City, Mexico

This is an observational, cohort study nested within a phase II, open-label, clinical trial designed to test if high-dose rifampin administered intravenously or orally would improve blood and CSF rifampin exposure in people with tuberculosis meningitis (TBM) in a population consisting predominantly of people living with HIV (PLHIV) receiving care in Uganda. In this manuscript, Carson Quinn and colleagues report the results of longitudinal neurocognitive assessments performed in 36 participants of said trial that survived the initial event of TBM and had at least 8 weeks of follow-up. Only a fraction of these (n=28) completed the neurocognitive evaluations 24 weeks after enrollment.

This is a small, but relevant study providing evidence that people surviving TBM may have significant cognitive impairments 8 and 24 weeks after having initiated treatment for tuberculosis and around 4 months after ART initiation. While the participants improved over time in general, the phenotypes of impairment were remarkably different at each timepoint: from a non-specific phenotype with moderate to severe impairments in several areas (including executive function, verbal learning, verbal memory; and speed of information processing) at week 8, to a severe impairment of predominantly fine motor and executive functions at week 24. Remarkably, the authors also observed high prevalence of depression in this population, that did not seem to decrease significantly over time, which contrasted with significant improvements in disability.

The article is well written, easy to follow, and the authors have provided, in my view, a coherent narrative of an important health problem with potential public health ramifications, on which not sufficient attention has been laid. The strength of the findings of the study is limited by the small sample size, relatively high attrition and short follow-up, and difficulties in measuring neurocognitive function, which the authors tried to address as best as possible and discussed in detail. Previous reviewers have pointed out several shortcomings, to which the authors responded adequately.

I just want to add that non-acknowledged limitation of this study, is that this is a secondary analysis of a randomized clinical trial, with strict inclusion and exclusion criteria, that may have

undiscussed implications for external validity, even locally. This is not a population study with a sample size or study population designed to answer the specific question that this analysis is trying to answer. Previous studies have shown important differences in sociodemographic characteristics and clinical outcomes between participants in clinical trials and people receiving care through routine clinical care. This does not undermine the relevance of this study, but needs to be acknowledged as a limitation.

Also, while I agree with their conclusion that their findings highlight the need for neurorehabilitation and management of depression in TBM survivors; I would only add that larger studies with longer-term follow-up are needed to better characterize neurocognitive function outcomes in people recovering of tuberculous meningitis.

**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?**
Partly

**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:*** Epidemiology of HIV care, therapeutic clinical trials

**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.**

Reviewer Report 04 March 2022

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**Deanna Saylor**
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Dr. Quinn and team have adequately addressed all of my previous concerns, and I believe the revised manuscript has improved in clarity and in a more streamlined message. I believe it represents a very important contribution to the TBM literature and congratulate the authors on this important work.

**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:*** Neurocognitive impairment in HIV, neuro-infectious diseases, neuroepidemiology and clinical neurology in sub-Saharan Africa

**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.**

**Version 1**

Reviewer Report 11 November 2021

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**Reuben Robbins**

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This is a well-written manuscript describing neurocognitive outcomes among a small sample of Ugandan adults with tuberculosis meningitis (TBM), most of whom were also HIV-infected. The study describes neurocognitive functioning at 8 and 24 weeks post enrollment in a prospective cohort, phase 2 label randomized trial for TBM. The authors found high rates of global and domain specific impairment at 8 weeks and slightly less rates of impairment at 24 weeks. This study makes an important contribution to our understanding of neurocognitive functioning in HIV-associated TBM.

There are four concerns:

1. The title refers to HIV-associated TBM, yet two participants in the study do not have HIV. Why include them? Do they differ in any way from the HIV+ participants, whether demographically or neurocognitively?

2. The authors use the phrase "population mean" and "population norms" to describe the control sample's performance on the neuropsychological test battery. This is misleading, as a sample of 100 is not usually referred to as a population norm. Population based norms typically have sample sizes in the (many) thousands. These are control-based or convenience sample-based norms. They may or may not reflect the true Ugandan population performance on these tests.

3. Since the sample of TBM patients receive the same battery of tests twice, could some of the improvements be explained by practice effects? Did the control sample, from which norms were derived, complete the battery of neuropsychological tests more than once? And if so, do the norms take practice effects into account. If not, this is a limitation and must be noted as such.

4. There is little detail as to how the neuropsychological tests were adapted for Luganda. One of the source articles (citation #40) says, "All the tests had their instructions and content translated into Luganda." There is a growing body of literature describing some challenges of simple forward translations of neuropsychological tests. Without extensive cultural adaption that includes assessment of test acceptability and understandability that follow guidelines set forth by the International Test Commission and American Educational Research Association, it is not clear how "valid" the tests are for Uganda. That being said, because the battery has been used extensively there, the lack of information and procedures regarding adaptation can be noted as a limitation, and thus the tests may not accurately measure the cognitive domains they purport to and could bias performance downwards.

**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:*** Neuropsychology, HIV, test development and adaptation, international research

**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 25 Feb 2022

**Carson Quinn**,

Dear Dr. Robbins,
We appreciate your thoughtful review and the recommendations you have made for improving the manuscript. We will respond to each of your comments below. A new revised version taking into account yours and Dr Saylor's comments has been submitted and should be available for review shortly.

1. *The title refers to HIV-associated TBM, yet two participants in the study do not have HIV. Why include them? Do they differ in any way from the HIV+ participants, whether demographically or neurocognitively?*
    - You bring up a very important point about our study population, and a manner in which the manuscript suffered from imprecise wording. In designing the study, we endeavored to enroll a population that was representative of the TB Meningitis burden in Uganda. Past studies of neurocognitive outcomes of TBM have enrolled patients from southern and southeast Asia, and we wanted to ensure patients in Sub-Saharan Africa were represented in this literature. This Ugandan TBM population is largely, but not entirely, an HIV-positive population. However, as you state, our title and other high-level descriptions of the study refer to the cohort as "HIV-positive" which is misleading. We have therefore changed our language to reflect that this is a "primarily HIV-positive cohort" and our goal was more so to reflect the population of TBM survivors in Uganda. Because there were only 2 HIV-negative participants it is challenging

to definitively comment on group differences in outcomes or demographics. They were demographically similar to the cohort besides one being in the youngest quartile of age, and in outcomes they differed more from one another than from the cohort as a whole with one participant doing relatively well and the other poorly.

2. *The authors use the phrase "population mean" and "population norms" to describe the control sample's performance on the neuropsychological test battery. This is misleading, as a sample of 100 is not usually referred to as a population norm. Population based norms typically have sample sizes in the (many) thousands. These are control-based or convenience sample-based norms. They may or may not reflect the true Ugandan population performance on these tests.*
    - Thank you for pointing out this imprecise language on our part. We have adjusted the wording to refer to the “control group mean” rather than population mean and added the limited size of our control group as a limitation.
3. *Since the sample of TBM patients receive the same battery of tests twice, could some of the improvements be explained by practice effects? Did the control sample, from which norms were derived, complete the battery of neuropsychological tests more than once? And if so, do the norms take practice effects into account. If not, this is a limitation and must be noted as such.*
    - This is another excellent point. Practice effects certainly could have played a role, as the control sample to which we have normed the results did not have participants take the battery more than once. However, we hoped to lessen these effects by designing the study with a relatively long time between test administrations (4 months). However, as it could have still played a role, we have added this as a limitation to the study.
4. *There is little detail as to how the neuropsychological tests were adapted for Luganda. One of the source articles (citation #40) says, "All the tests had their instructions and content translated into Luganda." There is a growing body of literature describing some challenges of simple forward translations of neuropsychological tests. Without extensive cultural adaption that includes assessment of test acceptability and understandability that follow guidelines set forth by the International Test Commission and American Educational Research Association, it is not clear how "valid" the tests are for Uganda. That being said, because the battery has been used extensively there, the lack of information and procedures regarding adaptation can be noted as a limitation, and thus the tests may not accurately measure the cognitive domains they purport to and could bias performance downwards.*
    - Thank you for bringing up this important point that is essential to consider when undertaking neurocognitive testing on non-English speaking participants from cultural contexts unlike those of the participants the test was initially designed for. We were unable to obtain information on exactly how the tests were adapted for Luganda initially by our collaborators. However, this battery of tests, and the International HIV Dementia Scale one which they are based, have been validated in past studies with Luganda-speaking Ugandan participants. Other studies have also assessed differences in test results between English and Luganda-speaking participants and found them to be minimal. For these reasons, this battery is commonly used in Uganda, and we

are reassured that language differences are unlikely to be significantly biasing our results. This is now better-explained in the manuscript with appropriate citations, and added as a limitation.

*Addendum to Response to Reviewer 1*
After further consideration of the matter of treatment arm differences in outcomes, we have determined that inclusion of further data on neurocognitive outcomes between the different treatment arms would be counterproductive, as the intention of the study was to describe neurocognitive outcomes in TB meningitis not to test the impact of the trial treatment. With the low numbers in each group, no meaningful conclusions could be expected to be drawn. Differences in functional status and other clinical outcomes between the trial arms are included in the manuscript for the parent trial. This is now expounded upon further in the manuscript text, and noted as a limitation inherent in our small cohort.

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

Reviewer Report 20 September 2021

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**Deanna Saylor**
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Quinn, et al highlight the knowledge gap regarding neurocognitive and psychiatric outcomes in people with HIV (PWH) who survive TB meningitis (TBM) overall and in sub-Saharan Africa in particular and set out to determine these outcomes in a group of PWH TBM survivors in Uganda. They found nearly uniform neurocognitive impairment at 8 weeks, which improved but remained substantial at 24 weeks. In particular, verbal learning and memory, processing speed, and executive function were impaired as well as multiple domains of motor function. The authors also found high rates very high rates of depression at 8 weeks, and this did not change significantly at 24 weeks. Overall, this is an important study trying to address an important knowledge gap in the literature. However, there are important methodological and analytical decisions that were made which need to be further explained and/or reconsidered in order to further strengthen the paper. Finally, I believe a more nuanced consideration of the limitations of the study is also needed. Specifically:

1. The authors state that the goal of the study was to understand post-TBM depression and cognitive outcomes in PWH living in sub-Saharan Africa. As such, it is surprising to me that the two HIV-uninfected participants were included in the study. These patients are likely to be quite different than those with HIV co-infection and increase the heterogeneity of the

population and data obtained. Given that they represent such a small proportion of the study cohort, I would strongly consider excluding them from the analysis or, at minimum, provide a strong justification for why they should remain.

2. Please expand more on how the possibility that the treatment received in the trial may have contributed to neurocognitive and/or depression outcomes was assessed. It may also be prudent to list the possibility that this was not able to be completely accounted for in the analysis due to small sample sizes in each treatment group as a possible limitation.

3. Please provide greater detail about the demographics of HIV-uninfected controls used for neurocognitive norms. Was the language of administration similar? Were education levels distributed somewhat similarly? This is important in understanding the validity of the normative data used for the study cohort and may also be a limitation of the study.

4. Please justify the decision to include patients who were too sick to complete the analyses in the neurocognitive outcomes but not the depression outcomes. Do the authors really think including these patients is representative of the typical neurocognitive deficits after TBM? At a minimum, it would be great to present more detail about how results differed when excluding them.

5. It appears there is a significant number of participants with missing data on functional outcome measures at 8 weeks. Can this be explained?

**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?**
Partly

**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:*** Neurocognitive impairment in HIV, neuro-infectious diseases, neuroepidemiology and clinical neurology in sub-Saharan Africa

**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 15 Oct 2021

**Carson Quinn**,

Dear Dr. Saylor,
We appreciate your thoughtful review and the recommendations you have made for improving the manuscript. We will respond to each of your comments below:

1. *The authors state that the goal of the study was to understand post-TBM depression and cognitive outcomes in PWH living in sub-Saharan Africa. As such, it is surprising to me that the two HIV-uninfected participants were included in the study. These patients are likely to be quite different than those with HIV co-infection and increase the heterogeneity of the population and data obtained. Given that they represent such a small proportion of the study cohort, I would strongly consider excluding them from the analysis or, at minimum, provide a strong justification for why they should remain.* You bring up a very important point about our study population, and a manner in which the manuscript suffered from imprecise wording. In designing the study, we endeavored to enroll a population that was representative of the TB Meningitis burden in Uganda. Past studies of neurocognitive outcomes of TBM have enrolled patients from southern and southeast Asia, and we wanted to ensure patients in Sub-Saharan Africa were represented in this literature. This Ugandan TBM population is largely, but not entirely, an HIV-positive population. However, as you state, our title and other high-level descriptions of the study refer to the cohort as "HIV-positive" which is misleading. We will therefore change our language to reflect that this is a "primarily HIV-positive cohort" and our goal was moreso to reflect the population of TBM survivors in Uganda.

2. *Please expand more on how the possibility that the treatment received in the trial may have contributed to neurocognitive and/or depression outcomes was assessed. It may also be prudent to list the possibility that this was not able to be completely accounted for in the analysis due to small sample sizes in each treatment group as a possible limitation.* You are correct in wondering how the trial treatment could have impacted neurocognitive outcomes in survivors, and it is a question that we intend to study further in the future. This study was not powered to answer this question, and the numbers in each of the treatment groups that survived to neurocognitive assessment follow-up is too low to meaningfully comment on the differential impact of the trial treatments. However, in these small groups, there did not appear to be any significant difference in the summary neurocognitive score between the treatment groups. We will ensure that this data is provided in the revised manuscript (it is currently present in the extended data that is available), and comment on this accordingly as a limitation of the manuscript.

3. *Please provide greater detail about the demographics of HIV-uninfected controls used for neurocognitive norms. Was the language of administration similar? Were education levels distributed somewhat similarly? This is important in understanding the validity of the normative data used for the study cohort and may also be a limitation of the study.* The

HIV-negative control participants are cohorted by age and education in the same groups as our study population to allow for norming of the study data. The tests were also performed in Luganda and English according to participant preference for both the controls and study population. We will provide more complete demographics beyond this in the revised manuscript.

4. *Please justify the decision to include patients who were too sick to complete the analyses in the neurocognitive outcomes but not the depression outcomes. Do the authors really think including these patients is representative of the typical neurocognitive deficits after TBM? At a minimum, it would be great to present more detail about how results differed when excluding them.* The decision to include participants too sick to complete the neurocognitive assessment was one of the major challenges in designing this study; while both options (to include or not to include) had drawbacks, I will provide our rationale here and comment further in the revised manuscript. Our intended population was survivors of TB meningitis -- many of these survivors are unfortunately very functionally impaired and remain with a significant burden of chronic symptoms from their TBM. To exclude these patients would be to represent TBM as a less morbid disease than it in fact is. It is true that the imputed values for the neurocognitive assessments in these patients aren't particularly meaningful on an individual level, and do not further our goal of demonstrating a typical phenotype of impairment in TBM. However, they do serve to accurately represent the degree of neurocognitive impairment frequently present in survivors of TBM. We did perform a sensitivity analysis showing that inclusion of these patients did not importantly impact the neurocognitive domains affected. We will be sure to add this data to the revised manuscript and explain this limitation further. Furthermore, we hope for this study to contribute to a standardized format allowing cross-comparison for future studies of neurocognitive impairment in TBM, which may have goals of investigating risk factors for impairment -- in which case inclusion of these more impaired patients is essential.

5. *It appears there is a significant number of participants with missing data on functional outcome measures at 8 weeks. Can this be explained?* Thank you for noting this. This Karnofsky functional score were missing in patients deemed too impaired to complete neurocognitive assessment; however, as those scores are in fact available, they will be added to the revised manuscript.

Thank you again for your many constructive comments. We intend to submit a revised manuscript after receiving a second review so as to respond to comments from both reviewers. I am hopeful that the revised manuscript appropriately addresses your concerns.
Sincerely,
Carson Quinn on behalf of the authors

***Competing Interests:*** None