Seizures in HIV-associated Cryptococcal Meningitis: Predictors and Outcomes

Katelyn A Pastick[1,2], Ananta S Bangdiwala[1], Mahsa Abassi[1,2], Andrew G Flynn[1], Bozena M Morawski[1], Abdu K Musubire[2], Prosperity C Eneh[1], Charlotte Schutz[3], Kabanda Taseera[4], Joshua Rhein[1,2], Kathy Huppler Hullsiek[1], Melanie R Nicol[1], Jose E Vidal[5,6], Noeline Nakasujja[2], Graeme Meintjes[3,7], Conrad Muzoora[4], David B Meya[1,2], David R Boulware[1]

Affiliations:

[1] *University of Minnesota, Minneapolis, MN, USA*

[2] *Infectious Diseases Institute, Makerere University, Kampala, Uganda*

[3] *Wellcome Center for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of Infectious Disease and Molecular Medicine and Department of Medicine, University of Cape Town, South Africa*

[4] *Mbarara University of Science and Technology, Uganda*

[5] *Instituto de Infectologia Emilio Ribas, São Paulo, São Paulo, Brazil*

[6] *Divisão de Moléstias Infecciosas e Parasitárias, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*

[7] *Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, South Africa*

Corresponding Author: Katelyn A Pastick, Infectious Diseases Institute, P.O. Box 22418, Kampala, Uganda. Email: past0064@umn.edu

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Summary: Seizures are common in cryptococcal meningitis. We identified several clinical risk factors related to seizures and found that seizures were associated with an

increased risk in mortality and poor neurocognitive outcomes in HIV-infected persons with cryptococcal meningitis.

Abstract

Background: Seizures commonly occur in patients with cryptococcal meningitis, yet risk factors and outcomes related to seizures are not well described.

Methods: We performed post-hoc analyses on participants prospectively enrolled in three separate HIV-associated cryptococcal meningitis clinical trials during 2010–2017. Documentation of seizures at presentation or during hospitalization, and anti-seizure medication receipt identified participants with seizures. We summarized participant characteristics by seizure status via Kruskal-Wallis and Chi-square tests. Cox proportional hazards models analyzed the relationship between seizures and mortality. We compared mean quantitative neurocognitive performance Z (QNPZ-8) scores, and individual domain z-scores, at 3-months using independent *t*-tests.

Results: Among 821 HIV-infected cryptococcal meningitis participants, 28% (231/821) experienced seizures: 15.5% (127/821) experienced seizures at presentation, and 12.7% (104/821) experienced incident seizures. Participants with seizures at presentation had a significantly lower Glasgow coma scale (GCS<15) (p<0.001), CD4 count (<50 cells/mcL) (p=0.02), and higher cerebrospinal fluid (CSF) opening pressure (>25 cm H_2O) (p=0.004) when compared with participants who never experienced seizures. CSF fungal burden was higher among those with seizures at presentation (125,000 *Cryptococcus* colony forming units (CFU)/mL CSF) and with seizures during follow-up (92,000 CFU/mL) compared with those who never experienced seizures (36,000 CFU/mL, p<0.001). Seizures were associated with increased 10-week mortality (adjusted Hazard Ratio = 1.45, 95%CI: 1.11, 1.89). Participants with seizures had lower neurocognitive function at 3-months (QNPZ-8 = -1.87) compared with those without seizures (QNPZ-8 = -1.36; p<0.001).

Conclusions: Seizures were common in this HIV-associated cryptococcal meningitis cohort and were associated with decreased survival and neurocognitive function.

Introduction:

Cryptococcal meningitis is one of the most common HIV-related opportunistic infections in sub-Saharan Africa with mortality rates upward of 70% in routine care [1]. Patients with cryptococcal meningitis often present with nonspecific complaints such as headache, fever, altered mental status, nausea, and vomiting. Some patients with cryptococcosis however, present with more severe neurological complications, including a variety of neuro-ophthalmologic symptoms and seizures [2-5]. These complications are presumptively due to high intracranial pressure and/or brain parenchymal involvement (i.e. meningoencephalitis) [6,7].

Seizures can be a presenting symptom or sequela of central nervous system infections. Approximately 16–34% of patients recently diagnosed with various forms of meningitis will experience seizures during disease progression [5,8-10]. In cryptococcal meningitis, seizures are present in 8-29% of HIV-negative and 6-35% of HIV-infected patients [5,11-17]. Presently, there are no criteria to predict which cryptococcal meningitis patients will develop seizures. Furthermore, the use of available anti-seizure medications in resource-limited settings is often complicated by drug-drug interactions with HIV antiretroviral or tuberculosis (TB) medicines, hindering the safe and effective use of anticonvulsants in controlling seizures [18-20].

In HIV-negative cryptococcal, bacterial, and tuberculous meningitis cohorts, seizures have generally been associated with significant morbidity and mortality, longer hospital stays, and poorer outcomes [5,10,21]. To our knowledge, these findings have not been described in HIV-associated cryptococcal meningitis patients. In this analysis of three HIV-associated cryptococcal meningitis cohorts, we report the observed prevalence of seizures, evaluate associations between clinical characteristics in relation to seizure risk,

characterize all-cause 10-week mortality and 3-month neurocognitive outcomes related to seizures, and discuss commonly used anti-seizure medications and associated drug-drug interactions.

Methods:

Patient Population

Participants with HIV-associated cryptococcal meningitis were prospectively enrolled in three separate clinical trials in Uganda and South Africa from November 22, 2010 to May 31, 2017. The first trial enrolled ART-naive, HIV-infected participants with no previous history of cryptococcal meningitis (NCT01075152, COAT) [22]; and the latter two trials enrolled ART-naïve and ART-experienced HIV-infected participants, and followed those with a previous history of cryptococcosis (NCT01802385, ASTRO-CM) [23,24].

Participants in all three cohorts were ≥18 years of age and had documented HIV-1 infection. Pregnant or breast-feeding women were excluded from all studies. Cryptococcal meningitis was initially determined by a positive cerebrospinal fluid (CSF) cryptococcal antigen assay (CrAg) (LFA, Immy, Norman OK) and confirmed with CSF culture. Participants in all three trials received combination induction therapy with 0.7–1.0 mg/kg amphotericin B deoxycholate and 800 mg/day fluconazole. Participants enrolled in the ASTRO-CM pilot study additionally received 100–400 mg/day of open-label sertraline [23]. Participants enrolled in the ASTRO-CM double-blind randomized clinical trial received either 400 mg sertraline or placebo for two weeks, followed by 200 mg/day sertraline or placebo for 12 weeks, and a tapered sertraline or placebo dose over three weeks thereafter [24]. Follow-up time for participants was 12, 18, or 46 weeks

depending on study cohort. For purposes of this post-hoc analysis, participants with first-episode cryptococcal meningitis, who were eligible for randomization or inclusion into the parent trials, were included in these analyses, as long-term follow-up data existed.

In all three cohorts, "seizure" was defined by motor seizures, as electroencephalograms (EEGs) were not available. "Baseline seizure" was defined as any seizure event between symptom onset and study enrollment among all study participants. "Incident seizure" was defined as any seizure event that occurred during hospitalization or during the outpatient follow-up period among participants who did not experience baseline seizures. "Any seizure" was defined as baseline or incident seizures during follow-up among all participants.

Data capturing seizure events were collected at presentation and prospectively on case report forms. Recorded seizure events by clinicians on case report forms were predominantly subjective generalized seizures, but study staff did occasionally report events of impaired awareness suspicious for non-motor seizures. Administration of anti-seizure medication(s) (carbamazepine, levetiracetam, phenobarbital, phenytoin, and valproate) was also used as a proxy for seizure events.

Statistical Analysis

Demographic and clinical characteristics at cryptococcal meningitis disease presentation were summarized and compared by seizure status via Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables. Among those who did not experience a baseline seizure, a Cox proportional hazards model estimated hazard of incident seizure and evaluated potential seizure predictors from among the following

baseline covariates: study cohort, age, sex, Glasgow Coma Scale (GCS) <15, lumbar puncture opening pressure > 25 cm H_2O, CSF fungal burden (quantitative cryptococcal culture), and CD4<100 cells/μL.

We evaluated 2- and 10-week mortality between participants who had and had not experienced baseline seizures via a log-rank test depicted with Kaplan-Meier curve. Cox proportional hazards models were used to estimate the hazard of mortality by baseline seizure and considering seizures as a time-dependent covariate. Final models were adjusted for study cohort, baseline GCS, CSF opening pressure, CSF fungal burden, and CD4<100 cells/μL.

The relationship between any seizure before 3-months and neurocognitive function was assessed by comparing mean quantitative neurocognitive performance Z (QNPZ-8) scores at 3-months (previously described [25,26]) using an independent *t*-test. The QNPZ-8 score was calculated as the mean of domain-specific raw scores, including Symbol Digit Modality, WHO-UCLA Auditory Verbal Learning, Verbal Fluency, Color Trails 1 and 2, Groove Pegboard (mean of dominant and non-dominant), and Finger Tapping. Scores were stratified on age and education level, and standardized based on the sample mean and standard deviation of an HIV-negative cohort [27]. The domain-specific tests were similarly compared between baseline seizure status. Patients who were scheduled to perform the tests and were too ill to complete a test were assigned a value for that missed test equal to 2 standard deviations less than the mean z-score for the cohort. Scores without imputation were also assessed. Neurocognitive testing in the COAT trial was only performed in Kampala, as there was an HIV-negative language-specific control group, which existed to establish population norms. Participants elsewhere were therefore

not scheduled for neurocognitive testing and subsequently were not included in this part of the analysis. All neurocognitive assessments were conducted by a local study nurse who received in depth training related to the specific battery of tests.

P-values <0.05 were considered statistically significant. No adjustments were made for multiple testing. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results:

From 1716 potentially eligible HIV-infected participants with suspected meningitis, 66% (1132/1716) had confirmed cryptococcal meningitis with positive CSF CrAg. Based on individual parent study inclusion criteria, 821 participants with first episode cryptococcal meningitis were included in this cohort analysis. Of the 895 excluded, 220 had first-episode cryptococcal meningitis, were screened, but not enrolled into the parent trials based on eligibility criteria (10% with baseline seizures), 91 had a prior history of cryptococcal meningitis (13% with baseline seizures), and 44 were found to have positive serum CrAg, but had a negative CSF CrAg (5% with baseline seizures). An additional 100 participants had definite/probable TBM (15% with baseline seizures), 28 had bacterial meningitis (36% with baseline seizures), 6 had confirmed viral meningitis (0% with baseline seizures), and 406 had unknown/other diagnosis (14% with baseline seizures) (**Figure 1**).

Overall, 15.5% (127/821) of participants with first episode cryptococcal meningitis included in this study presented with seizures either prior to or at the time of cryptococcal meningitis diagnosis ("baseline" seizure). An additional 12.7% (104/821) of participants

who did not present with baseline seizures experienced incident seizures during follow-up.

Higher baseline CSF quantitative culture fungal burdens occurred among participants who experienced either baseline seizures (median 125,000 *Cryptococcus* CFU/ml [IQR: 12,400–567,000]) or incidence seizures (92,000 CFU/ml [IQR: 6,883–360,000]) compared with those who did not experience seizures (36,000 CFU/ml [IQR: 1,011–230,000]; p<0.001). Participants who had seizures at baseline were more likely to have a baseline GCS <15 (61%) when compared with participants who later experienced incident seizures (36%) or did not experience seizures at all (36%; p<0.001). Participants who experienced baseline seizures were also more likely to have CD4 counts <50 cells/μL (84%) when compared with those who later experienced incident seizures (74%) or had no seizures (72%; p=0.02). Those who experienced seizures at baseline more frequently had elevated baseline CSF opening pressures of >25cm H_2O (68%) compared with those who later experienced incident seizures (54%) or had no seizures (51%; p=0.004). Age, sex, ART status, CSF white cell count, and CSF protein did not differ between those with baseline seizures, those that later experienced incident seizures, or those without seizures in this cohort (**Table 1**). Severe hyponatremia (sodium <120 mEq/L) was not significantly different between those with or without seizures at baseline (baseline seizure: 7%, incident seizure: 2%, no seizure: 5%, p=0.41), nor was it significantly different between those with baseline seizures and those with incident seizures (p=0.17).

Of those who experienced incident seizures, the median time to seizure event from meningitis diagnosis was 9 days (IQR: 4–36 days). In a fully adjusted model, sex, higher

baseline fungal burdens, and enrollment into later study cohorts (2013–2017) were found to be significantly associated with incident seizures (**Table 2**). Women had a 62% higher hazard of incident seizure, but the confidence interval was wide (aHR= 1.62, 95%CI: 1.05-2.49, p=0.03). For every unit increase in $\log_{10}$ CFU/ml of CSF fungal burden, the risk of incident seizure was 16% higher (adjusted Hazard Ratio (aHR) = 1.20, 95%CI: 1.03–1.40; p=0.01). The risk of incident seizure in the ASTRO-CM study was 2.3 times that of participants in COAT (aHR 2.28, 95%CI: 1.23–4.23; p<0.01). Because of the large difference in incident seizure risk between study cohorts, we conducted analyses adjusting for sertraline administration in ASTRO-CM clinical trial. Sertraline was not statistically significant between seizure groups.

There was no significant difference in 2-week mortality for participants who ever experienced a seizure during follow-up compared to those who did not experience a seizure (aHR 1.06, 95%CI: 0.77–1.45). Mortality was high amongst all participants within the first two weeks (**Figure 2**). More participants with baseline seizures died by 10 weeks (50%, 63/126) than those without baseline seizures (40%, 271/682) (log-rank p=0.02). Participants who experienced any seizure had a significantly higher risk of 10-week mortality than participants who had never experienced a seizure at any point during follow-up in the time-dependent analysis (aHR 1.40, 95%CI: 1.06–1.84) (**Table 3, Figure 2**).

Anti-seizure medications were prescribed at or within one week of the first seizure event for 54% (125/231) of participants. Of those who received anti-seizure medications, 62% (77/125) received valproic acid, 31% (39/125) received phenytoin, 6% (8/231) received carbamazepine, and <1% (1/231) received phenytoin and valproic acid at their

first seizure event. The median time on any anti-seizure medication during follow-up was 13 days (IQR: 6–26, max 185 days). Anti-seizure medications were not routinely prescribed in cases where participants had isolated seizure events that were self-reported and/or not witnessed by medical staff nor when seizures were controlled with the initial benzodiazepine medications. A subset of participants who experienced seizures may have died prior to the initiation of anti-seizure medication, contributing to the low percentage.

Overall, 292 participants completed at least a portion of the neurocognitive assessment at 3-months. Cryptococcal meningitis survivors' neurocognitive QNPZ-8 scores were 1.27 standard deviations below the average for an HIV-negative person with the same age and education level. Participants who had experienced any seizure by three months had significantly lower QNPZ-8 scores when compared to participants who had not experienced a seizure ($p<0.001$). This difference remained statistically significant when adjusted for study cohort, baseline GCS, CSF opening pressure, CSF fungal burden, and CD4<100 cells/μL. Persons who had experienced any seizure had lower neurocognitive performances in executive function, language fluency, verbal learning and memory, fine motor, motor speed, and gross motor function. See **Supplemental Table 1** for additional information.

Discussion:

In this post-hoc analysis of three prospective studies, seizures occurred in 28% (231/821) of participants with HIV-associated cryptococcal meningitis, and seizures were associated with increased 10-week mortality. Previous studies in HIV-negative cryptococcal meningitis cohorts have reported a seizure incidence between 8–29% [5,12,13].

In our cohort, a similar proportion of participants experienced baseline and incident seizures (15.5% vs. 12.7%). Baseline seizures additionally occurred at a similar frequency to screened tuberculosis meningitis patients (15%) and participants with a prior history of cryptococcal meningitis (13%), but less than that of bacterial meningitis participants (36%).

Among cryptococcal meningitis patients, altered mental status (GCS<15) is a known independent predictor of mortality and is associated with increased intracranial pressure [28,29]. We found that persons presenting with seizures at baseline were also more likely to present with a GCS<15 and increased intracranial pressure. Increased CSF fungal burden was another risk factor for seizures; we postulate that high CSF fungal burden is also likely associated with greater extension of cryptococcal infection throughout the cerebral parenchyma, predisposing the presence of convulsions [6,7].

In our cohort, mortality was high amongst all participants with cryptococcal meningitis within the first two weeks of treatment. This likely explains why we did not observe an increased risk of mortality at two weeks when comparing those who experienced baseline seizures with those who did not experience baseline seizures in the adjusted model. When treating seizures as a time-dependent covariate, thereby including participants who experienced incident seizures during follow-up, we saw an increased 10-week mortality risk, even after adjusting for study, baseline opening pressure, GCS<15, CSF fungal burden, and CD4 <100 cells/μL. Incident seizures following the first two weeks of cryptococcal meningitis induction therapy thereby pose a continual threat to patients in their recovery.

Survivors who experienced any seizures had worse neurocognitive performance at three months when compared with survivors without any seizures. While QNPZ-8 scores tend to improve with appropriate cryptococcal meningitis treatment at six months [25], it is unknown if seizures impact neurocognitive recovery. Future work assessing long-term neurocognitive outcomes is warranted to determine if there are any residual neurocognitive impairments related to seizures during cryptococcal meningitis.

In our cohort of cryptococcal meningitis participants with seizures, carbamazepine, phenytoin, and valproic acid were the most commonly prescribed anti-seizure medications at time of first seizure event. Phenytoin, valproate, and carbamazepine all undergo hepatic metabolism by the cytochrome p450 (CYP450) system and are therefore susceptible to drug-drug interactions when co-administered with CYP450 inhibitors or inducers [30]. This includes many antiretrovirals, antifungals, antimycobacterials, and antimalarials commonly used in this population (see **Supplemental Table 2**) [18,30-33]. Of the more commonly used anti-seizure medications in resource-limited settings, levetiracetam has the lowest risk of potential drug-drug interactions, yet, availability and cost may be prohibitive [19]. Valproate is less affected by drug-drug interactions when compared to carbamazepine and phenytoin, and may be a suitable alterative if applicable. In the treatment of cryptococcal meningitis, amphotericin B deoxycholate related nephrotoxicity is common and may result in the impaired renal clearance of phenobarbital, levetiracetam, and valproate [30]. Special consideration of anti-seizure medications should therefore be made in cryptococcal meningitis patients with amphotericin-related renal dysfunction [34].

Several important limitations exist within this cohort analysis. First, the prevalence of seizures was likely underreported. Observed seizures were limited mainly to motor seizures as opposed to non-motor seizures, and a greater proportion of participants may have experienced non-motor seizures that were not observed or detected since EEGs were not available. Second, seizure events were not always directly observed, and events that were not in fact seizures may have been classified as seizures, resulting in possible misclassification. Third, ongoing seizures and subsequent interictal periods may have influenced neurocognitive testing. While neurocognitive testing was performed three months after acute hospitalization and most seizures occurred during the initial hospitalization, multiple factors could additionally influence outcomes, including possible subclinical seizures or poor adherence to or sub-therapeutic levels of anti-seizure medication. Lastly, while no participant had a known history of prior epilepsy, the possibility remains.

When examining risk factors for incident seizures, later study cohorts were significantly associated with increased risk. This likely was due to increased awareness of seizures in the later study cohorts, in addition to improved detection and reporting by more experienced study staff. Inflammatory immune reconstitution syndrome (IRIS) has not been evaluated in this study, so its contribution to incident seizures is unknown.

While it is believed that approximately 2–20% of HIV seropositive persons will experience seizures post HIV-diagnosis, these seizures are thought to be largely attributable to opportunistic central nervous system infections, as opposed to primary HIV infection [35,36]. Acute onset seizures in this cohort were presumed to be secondary to cryptococcal infection because of diagnostic testing and other meningeal symptoms.

However, due to the high prevalence of HIV-related opportunistic infections, other secondary opportunistic infections may have contributed to seizures [37-41]. The short median time (9 days [4-6 days]) to incident seizures from cryptococcal meningitis diagnosis dramatically reduces this possibility, but the lack of diagnostics and imaging studies likely contributed to under diagnosis of other clinical causes of seizures.

Overall, seizures were common in this cohort of HIV-infected cryptococcal meningitis participants and were associated with an increased risk of 10-week mortality and poor neurocognitive outcomes at 3-months. Fungal burden was identified as a potential clinical risk factor that may be valuable in the identification of patients at risk for the development of seizures during treatment for cryptococcal meningitis. Future work related to the detection and the causes and pathophysiology of seizures in this population is warranted given the high risk of mortality. Anti-seizure medications should be prescribed with care amongst this patient population due to existing drug-drug interactions and possible impaired renal clearance of such medications due to amphotericin B toxicity.

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Table 1. Demographic and Clinical Parameters by Baseline Seizure

	Baseline seizure	Incident seizure	No seizure	
	Median (IQR) or N (%)	**Median (IQR) or N (%)**	**Median (IQR) or N (%)**	**P-value[1]**
N	127 (15%)	104 (13%)	590 (72%)	
Cohort				0.13
2010-2012 COAT	30 (14%)	21 (10%)	163 (76%)	
2013-2014 ASTRO Pilot	16 (11%)	22 (15%)	111 (74%)	
2015-2017 ASTRO-CM	81 (18%)	61 (13%)	316 (69%)	
Demographics				
Age, years	34 [29, 40]	36 [29, 42]	35 [30, 40]	0.92
Women	55 (43%)	46 (44%)	233 (39%)	0.53
Glasgow Coma Score < 15	**78 (61%)**	**37 (36%)**	**209 (36%)**	**<0.001**
ART status				0.65
ART naïve	88 (69%)	63 (61%)	383 (65%)	
On ART ≤4 months	11 (9%)	11 (11%)	59 (10%)	
On ART >4 months	27 (21%)	29 (28%)	147 (25%)	
Unknown ART status	1 (1%)	1 (1%)	1 (0%)	
Symptom duration, days	21 [10, 30]	14 [12, 30]	14 [10, 30]	0.84
Blood results				
Absolute CD4 cells/μL	14 [6, 35]	17 [6, 58]	17 [7, 55]	0.07
CD4 < 50 cells/μL	**102 (84%)**	**73 (74%)**	**397 (72%)**	**0.02**
Sodium, mEq/L	128 [124, 133]	129 [126, 133]	130 [126, 134]	0.19
Glucose, mg/dL	110 [94, 119]	104 [86, 110]	100 [85, 115]	0.29
CSF results				
White cells/μL	<5 [<5, 45]	<5 [<5, 45]	<5 [<5, 56]	0.76
White cells < 5 cells/μL	71 (58%)	59 (60%)	323 (57%)	0.88
Protein, mg/dL	73 [36, 120]	62 [27, 124]	60 [24, 125]	0.28
Opening pressure, cm H_2O	**33 [21, 47]**	**27 [19, 45]**	**26 [17, 37]**	**0.002**
Opening pressure >25 cm H_2O	**77 (68%)**	**49 (54%)**	**261 (51%)**	**0.004**
***Cryptococcus* CFU/mL CSF**	**125,000 [12,400, 567,000]**	**92,000 [6,883, 360,000]**	**36,000 [1,011, 230,000]**	**<0.001**

*Percentages of each seizure group are displayed for categorical variables.

[1] P-values from Kruskal Wallis tests for continuous variables and Chi-square tests for categorical variables

Table 2. Hazard of Incident Seizure, Among Those Without a Baseline Seizure

Baseline characteristic*	HR (95% CI)	p-value
Cohort		
2010-2012 (COAT Trial)	Ref.	
2013-2017 (ASTRO Trials)	**2.28 (1.23, 4.23)**	**<0.01**
Age, years	1.00 (0.98, 1.03)	0.45
Women	**1.62 (1.05, 2.49)**	**0.03**
Glasgow Coma Score < 15	1.05 (0.65, 1.67)	0.84
CSF Opening Pressure, cm H_20	1.00 (0.99, 1.02)	0.27
Quantitative culture, log_{10} CFU/mL CSF	**1.20 (1.03, 1.40)**	**0.01**
CD4<100 cells/μL	1.02 (0.43, 2.38)	0.96

*Full model adjusted for study cohort, age, sex, baseline GCS<15, CSF opening pressure, CSF fungal burden, and CD4<100 cells/uL.

Table 3. Hazard of Mortality Related to Seizure Status

	2-Week Mortality	10-Week Mortality
	HR (95% CI)	HR (95% CI)
Baseline seizure vs. no baseline seizure		
Adjusted for Study	1.25 (0.86, 1.82)	**1.34 (1.02, 1.77)**
Adjusted for Study and baseline opening pressure, GCS, CSF fungal burden, CD4<100 cells/μL	0.92 (0.60, 1.42)	1.06 (0.77, 1.45)
Seizure as a time-dependent covariate		
Adjusted for Study	**1.43 (1.01, 2.02)**	**1.81 (1.42, 2.30)**
Adjusted for Study and baseline opening pressure, GCS, CSF fungal burden, CD4<100 cells/μL	0.99 (0.66, 1.49)	**1.40 (1.06, 1.84)**

*Results were similar when adjusted for ART status: on ART at diagnosis or ART naive. ART status was not included in the final model.

Figure Legends

Figure 1: Cohort Diagram. Depiction of participants enrolled in the parent studies and included in this analysis.

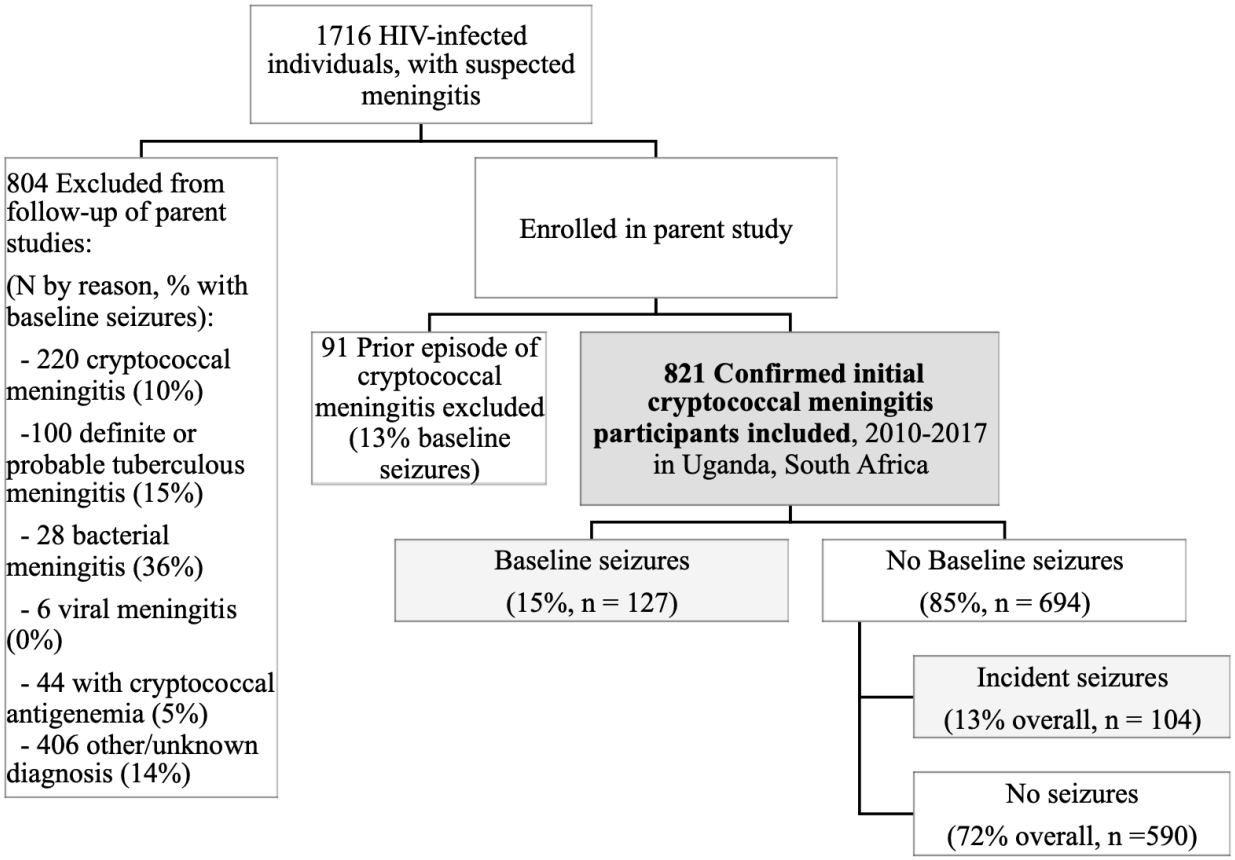

Figure 2: 10-week Survival Outcomes by Presence of Seizure at Hospital Presentation Among HIV-infected Persons with Cryptococcal Meningitis. More participants with baseline seizures died by 10 weeks (50%, 63/126) than those without baseline seizures (40%, 271/682) (log-rank p-value=0.02). Participants who experienced any seizure had a significantly higher risk of 10-week mortality than participants who had never experienced a seizure at any point during follow-up in the time-dependent analysis (aHR 1.45, 95% CI: 1.11–1.89).