745

Mortality due to HIV-associated Cryptococcal Meningitis in Botswana in the ART Era

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Introduction

Cryptococcal meningitis (CM) is a leading cause of death in HIV-infected individuals in Africa.

The incidence of CM has not reduced significantly despite expanding ART access in most African countries.

Case fatality rates of 20-35% with amphotericin-B based treatment have been reported in clinical trials conducted in Africa.

These are not representative of standard medical care due to the more intensive patient care in clinical trials.

We evaluated CM outcomes in a routine care setting utilizing centralized electronic medical records and robust civil registration data unique in Africa.

Methods

All laboratory-confirmed cases of CM at Princess Marina Hospital, Gaborone, from January 2012 to December 2014 were included in the study.

Cases were identified from a prospective register of all meningitis cases maintained at the hospital.

Standard treatment for CM was amphotericin B 1mg/kg plus fluconazole 800mg for 14 days.

Paper and electronic records were retrospectively interrogated to retrieve demographic and clinical data and in-hospital mortality.

Linkage with the National death registry allowed out of hospital deaths to be captured.

The primary endpoint was mortality at 1 year post antifungal induction.

Results

During the study period there were **283 episodes of CM** among 236 individuals (199 patients had a single episode, 37 patients had two or more episodes).

69% of patients were male and the median age was 36 (IQR 32-42) years. Median duration of hospitalization was 17 days (IQR 10-22).

At the time of death registry linkage in December 2015 **vital status was available at one-year for 93% (219/236) of patients.**

Median duration of follow-up in the remaining 17 patients was 25 (IQR 16-153) days.

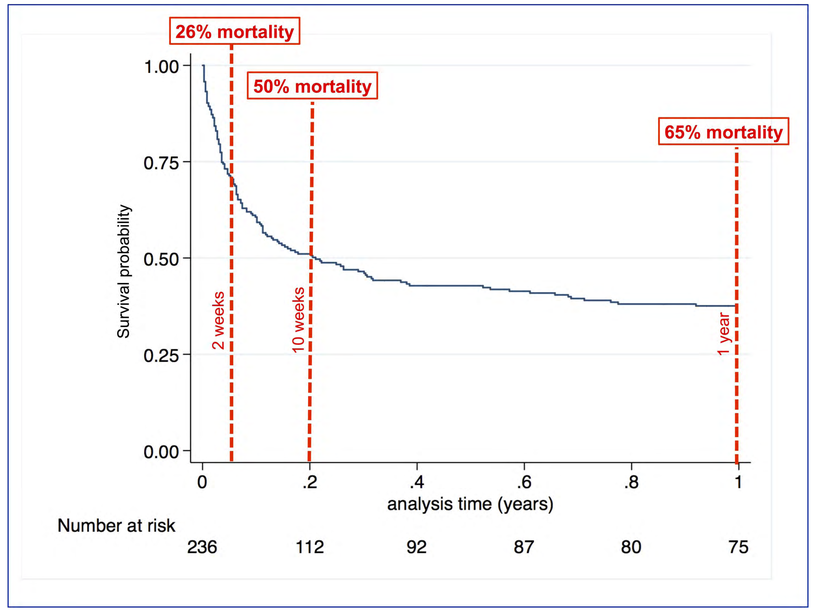


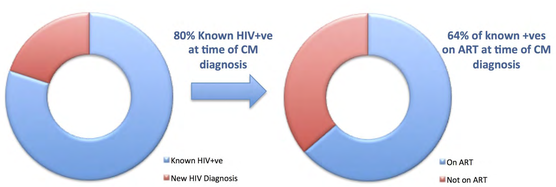
Figure 1. Kaplan Meier Survival Plot showing survival following initial episode of cryptococcal meningitis is 236 patients treated with amphotericin B 1mg/kg plus fluconazole 800mg daily under routine care conditions at Princess Marina Hospital, the main tertiary referral center in Botswana during 2012, 2013, and 2014.

Two-week mortality, 10-week mortality, and 1-year mortality were 26% (60/233), 50% (112/224), and 65% (142/219).

In a sensitivity analysis assuming all those lost to follow-up had died, this increased to 27% (63/236), 53% (124/236), and 67% (159/236).

The majority of patients had a known HIV diagnosis prior to presentation with CM, and many were already on ART.

Figure 2. Prior HIV diagnosis and ART status at CM presentation.



There was no association between ART status at CM presentation and mortality

42% of patients had an abnormal mental status at the time of CM presentation.

Table 1. Factors associated with mortality.

Variable	Survival	
	HR	95% CI
Abnormal mental status at presentation	1.63	1.1-2.5
CSF white cell count (<20cells/ml)	1.42	1.1-2.0
CD4 count (per 50 cell/µL increase)	0.84	0.7-0.9

Conclusions

Long-term outcomes in patients with HIV-associated CM treated with amphotericin B deoxycholate based regimens in routine care settings are extremely poor, with only 35% of patients surviving to one year even with universal ART access in one of the best-resourced health-care services in Africa.

Novel treatment strategies and alternatives to amphotericin B deoxycholate are urgently needed for effective management of patients with cryptococcal meningitis in resource poor settings.

Enhanced efforts are needed to prevent new cases and ensure early diagnosis and treatment of CM cases that do develop using the cryptococcal LFA – a cheap and effective point of care diagnostic test.

CRAG screening has the potential to markedly reduce CM incidence in Botswana given that 80% of the patients had a known HIV diagnosis at CM diagnosis.

References

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