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ORIGINAL RESEARCH

Prognostic implications of baseline anaemia and changes in haemoglobin concentrations with amphotericin B therapy for cryptococcal meningitis

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Objectives

Anaemia represents a common toxicity with amphotericin B-based induction therapy in HIV-infected persons with cryptococcal meningitis. We sought to examine the impact of amphotericin-related anaemia on survival.

Methods

We used data from Ugandan and South African trial participants to characterize the variation of haemoglobin concentrations from diagnosis to 12 weeks post-diagnosis. Anaemia severity was classified based on the haemoglobin concentration at cryptococcal meningitis diagnosis, and nadir haemoglobin values during amphotericin induction. Cox proportional hazard models were used to estimate 2- and 10-week mortality risk. We also estimated 10-week mortality risk among participants with nadir haemoglobin < 8.5 g/dL during amphotericin induction and who survived ≥ 2 weeks post-enrolment.

Results

The median haemoglobin concentration at meningitis diagnosis was 11.5 g/dL [interquartile range (IQR) 9.7–13 g/dL; $n = 311$] with a mean decline of 4.2 g/dL [95% confidence interval (CI) −4.6 to −3.8; $P < 0.001$; $n = 148$] from diagnosis to nadir value among participants with baseline haemoglobin ≥ 8.5 g/dL. The median haemoglobin concentration was 8.1 g/dL (IQR 6.5–9.5 g/dL) at 2 weeks, increasing to 9.4 g/dL (IQR 8.2–10.9 g/dL) by 4 weeks and continuing to increase to 12 weeks. Among participants with haemoglobin < 8.5 g/dL at diagnosis, mortality risk was elevated at 2 weeks [hazard ratio (HR) 2.7; 95% CI 1.5–4.9; $P < 0.01$] and 10 weeks (HR 1.8; 95% CI 1.1–2.2; $P = 0.03$), relative to those with haemoglobin ≥ 8.5 g/dL. New-onset anaemia occurring with amphotericin therapy did not have a statistically significant association with 10-week mortality (HR 2.0; 95% CI 0.5–9.1; $P = 0.4$).

Conclusions

Amphotericin induced significant haemoglobin declines, which were mostly transient and did not impact 10-week mortality. Individuals with moderate to life-threatening anaemia at baseline had a higher mortality risk at 2 and 10 weeks post-enrolment.

Keywords: amphotericin B, anaemia, cryptococcal meningitis, HIV

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Introduction

Anaemia is the most common haematological complication of HIV infection, affecting approximately 15% of individuals with advanced AIDS [1]. HIV-associated anaemia is an independent predictor of mortality, with an increased risk of death as haemoglobin levels decline [2–6]. Development of anaemia in HIV infection is multifactorial and includes decreased red blood cell production from the effects of chronic viral HIV infection, coinfection with opportunistic pathogens, nutritional deficiencies (e.g. deficiencies in iron, folic acid and vitamin B12), anaemia of chronic disease with inflammatory cytokine production, and myelosuppression caused by chemotherapeutic agents including antiretroviral therapy (ART) [7,8]. Furthermore, HIV-infected individuals with an AIDS-defining opportunistic infection are 4.5 times more likely to develop anaemia compared with individuals without an opportunistic infection [1].

Cryptococcal meningitis accounts for approximately 15% of AIDS-related mortality in sub-Saharan Africa [9–11]. The World Health Organization recommends 14 days of amphotericin B treatment in combination with flucytosine or fluconazole as induction therapy in cryptococcal meningitis treatment [12–14], which causes frequent clinically significant toxicities, including anaemia [15–17]. Amphotericin-associated anaemia is a subacute drug-related reaction resulting from blunted erythropoietin secretion and suppression of red blood cell production [18,19]. In a small cohort of 30 individuals treated with amphotericin for systemic fungal infections, 75% of individuals had a reduction of their haematocrit by 11% [20]. This degree of haematocrit decline could further compromise oxygen delivery to vital tissues in individuals who are already at an elevated risk of death from cryptococcal meningitis. Previous studies have evaluated the relationship between pre-existing anaemia and mortality in patients with cryptococcal meningitis. In a combined cohort of 501 HIV-infected persons with cryptococcal meningitis, a baseline haemoglobin concentration of < 7.5 g/dL prior to initiation of amphotericin therapy was independently associated with a threefold higher odds of mortality at 10 weeks [21].

In order to better understand the impact of anaemia on acute mortality in persons with HIV-associated cryptococcal meningitis receiving amphotericin, we characterized the relationship between amphotericin administration and haemoglobin levels during and after treatment. We also assessed the relationship between haemoglobin levels in individuals receiving amphotericin therapy and 2- and 10-week mortality.

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Methods

Data from the Cryptococcal Optimal ART Timing (COAT) trial (ClinicalTrials.gov: NCT01075152) and the pilot phase of the Adjunctive Sertraline for Treatment of Cryptococcal Meningitis (ASTRO-CM) trial (ClinicalTrials.gov: NCT01802385) were used for the analyses included herein. The COAT trial enrolled Ugandan and South African HIV-infected, ART-naïve individuals diagnosed with a first episode of cryptococcal meningitis who were randomized to either early or deferred ART initiation from 2010 to 2012, as described elsewhere [22]. The pilot phase of the ASTRO-CM trial was an open-label dose-finding study conducted from August 2013 to August 2014 in Kampala, Uganda. All COAT trial participants were ART-naïve at the time of meningitis diagnosis, whereas 45% of ASTRO participants were receiving ART at meningitis diagnosis and 5% (18 of 339) had received treatment for a prior episode of cryptococcal meningitis.

Participants were ≥ 18 years of age, and pregnant women were excluded. Cryptococcal meningitis was diagnosed by cerebrospinal fluid (CSF) cryptococcal antigen testing and confirmed via quantitative culture at Mulago National Referral Hospital, Kampala, Uganda (COAT and ASTRO-CM), Mbarara Hospital, Mbarara, Uganda (COAT), or G.F. Jooste Hospital, Cape Town, South Africa (COAT). Participants in both trials universally received combination induction therapy with amphotericin B deoxycholate (0.7–1.0 mg/kg/day) and fluconazole 800 mg/day. In addition, sertraline (100–400 mg/day) was administered to all participants in the ASTRO-CM pilot trial. All participants were followed for at least 12 weeks post-enrolment.

Haemoglobin levels were obtained from participants at the time of cryptococcal meningitis diagnosis in both trials, and among COAT trial participants only additionally at days 5, 7, 10 and 14 of amphotericin induction therapy and at weeks 4, 8, and 12. Anaemia severity was defined per the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) toxicity scale, version 2009 [23]. Moderate anaemia (grade 2) was defined as a haemoglobin concentration of 7.5–8.4 g/dL, severe anaemia (grade 3) as a haemoglobin concentration of 6.5–7.4 g/dL, and potentially life-threatening anaemia (grade 4) as a haemoglobin concentration < 6.5 g/dL.

Statistical analysis

Median haemoglobin concentration at diagnosis (both cohorts) and 14-day induction therapy nadir values (COAT only) were summarized. Change in haemoglobin concentrations from diagnosis to (1) the 14-day nadir haemoglobin value and (2) the end of induction therapy were evaluated via linear mixed models with random intercepts for an individual. Rates of change for these two periods were also evaluated across sexes and baseline haemoglobin statuses (haemoglobin ≥ 8.5 g/dL *vs.* < 8.5 g/dL) via interaction terms in linear mixed models. Additionally, differences in rates of haemoglobin change from diagnosis to 12 weeks post-diagnosis were evaluated across sexes and baseline anaemia severities via interaction terms of the linear mixed models among COAT participants only.

Composite exposures of grade 2–4 and 3–4 anaemia at diagnosis were used in Cox proportional hazards models to estimate 2- and 10-week mortality among COAT and ASTRO-CM participants. Fixed effects for ART status at diagnosis (receiving any ART in the last 30 days *vs.* not), prior history of treatment for cryptococcal meningitis, sex, age (≤ 50 years *vs.* > 50 years), $\log_{10}$ quantitative cryptococcal culture/mL CSF, and altered mental status (Glasgow coma score < 15 *vs.* not) were included in these models. Among those COAT participants with haemoglobin < 8.5 g/dL at diagnosis who survived at 2 weeks, the risk of 10-week mortality was assessed by nadir haemoglobin values during induction therapy. Kaplan–Meier curves displayed the 10-week mortality, with corresponding Cox model results. Analyses were conducted in STATA/IC 13.1 (StataCorp, College Station, TX, USA), and all results were evaluated against a two-sided alpha of 0.05.

Results

A total of 350 participants were enrolled in the two trials (177 in COAT and 173 in the pilot phase of ASTRO-CM). Of these, 339 participants had at least one haemoglobin measurement and were included in descriptive analyses, of whom 311 were included in survival analyses. Twenty-eight participants were missing a haemoglobin concentration at diagnosis and were excluded from the survival analyses. The baseline characteristics of these participants are described in Table 1. The median age was 36 years (IQR 30–41 years), and 41% (140 of 339) were women. At the time of diagnosis, 23% (78 of 338) of the participants were receiving ART. The median CD4 T-cell count was 20 cells/μL (IQR 8–70 cells/μL), and the median quantitative cryptococcal culture was 63 000 cfu/mL CSF (IQR 3900–316 000 cfu/mL CSF). The median baseline haemoglobin concentration in participants from both cohorts was 11.5 g/dL (IQR 9.7–13 g/dL; $n = 311$), with COAT participants having slightly lower baseline haemoglobin concentrations ($P = 0.04$). All COAT participants were ART-naïve. At diagnosis, 13% (41 of 311) of individuals presented with moderate to life-threatening anaemia (grade 2: $n = 23$; grade 3: $n = 11$; grade 4: $n = 7$).

Among COAT participants who received frequent longitudinal monitoring, plasma haemoglobin declined by a mean of 3.1 g/dL (95% CI −3.6, −2.6 g/dL; $P < 0.001$)

Table 1 Demographic and clinical characteristics of participants in the Cryptococcal Optimal ART Timing (COAT) and Adjunctive Sertraline for Treatment of Cryptococcal Meningitis (ASTRO-CM) trials

	COAT		ASTRO-CM		Combined		
Characteristic at diagnosis	*n*	*n* (%) or median [IQR]	*n*	*n* (%) or median [IQR]	*n*	*n* (%) or median [IQR]	*P*-value
Age (years)	177	35 [29, 40]	162	36 [31, 41]	339	36 [30, 41]	0.19
Women	177	84 (47)	162	56 (35)	339	140 (41)	0.02
Receiving ART	177	0 (0.0)	161	78 (48)	338	78 (23)	< 0.001
Prior diagnosis of cryptococcal meningitis	177	0 (0.0)	162	18 (11.1)	339	18 (5.3)	–
Glasgow coma scale < 15	176	47 (27)	162	56 (35)	338	103 (30)	0.12
Opening pressure (cm H_2O)	152	27 [18, 38]	149	30 [19, 48]	301	28 [18, 40]	0.12
Opening pressure > 25 cm H_2O	152	83 (55)	149	91 (61)	301	174 (58)	0.26
CSF culture ($\log_{10}$ cfu/mL)	168	5.1 [4.0, 5.6]	158	4.3 [3.1, 5.3]	326	4.8 [3.6, 5.5]	< 0.001
CD4 count (cells/μL)	175	23 [10, 74]	162	18 [7, 54]	301	20 [8, 70]	0.05
Haemoglobin (all) (g/dL)	149	11.4 [9.3, 12.9]	162	11.7 [10.1, 13.0]	311	11.5 [9.7, 13.0]	0.04
Haemoglobin (women) (g/dL)	73	10.5 [8.9, 11.9]	56	10.4 [9.2, 12.2]	129	10.5 [9.0, 12.0]	0.86
Hemoglobin (men) (g/dL)	76	11.8 [9.7, 13.6]	106	12.2 [10.7, 13.3]	182	12.1 [10.5, 13.5]	0.17
Haemoglobin < 8.5 g/dL	149	29 (19.5)	162	12 (7.4)	311	41 (13.2)	< 0.01

ART, antiretroviral therapy; IQR, interquartile range; CSF, cerebrospinal fluid.

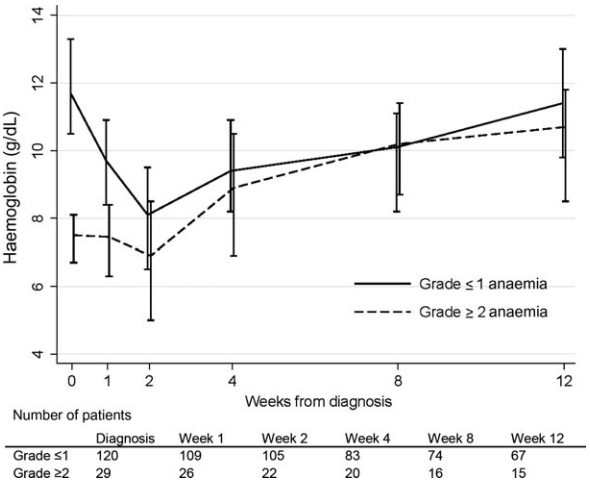

Fig. 1 Median (interquartile range (IQR)) haemoglobin concentrations from amphotericin B initiation to 12 weeks post-diagnosis among patients in the Cryptococcal Optimal ART Timing (COAT) trial, for patients with grade ≤ 1 anaemia *vs.* those with grade ≥ 2 anaemia (< 8.5 g/dL) at diagnosis. The overall median nadir haemoglobin concentration among all COAT participants was 7.4 g/dL (IQR 6.2, 8.9 g/dL). The median percentage change from baseline to nadir was a decrease of 31% (IQR −44, −22%).

from cryptococcal meningitis diagnosis to the end of induction therapy (14 days). Among patients enrolled in COAT who had haemoglobin ≥ 8.5 g/dL at diagnosis, there was a significant mean decline in haemoglobin concentration of 4.2 g/dL (95% CI −4.6, −3.8 g/dL; $P < 0.001$) from diagnosis to nadir values (Fig. 1); overall median nadir haemoglobin concentration was 7.4 g/dL (IQR 6.2–8.9 g/dL) during the first 14 days of cryptococcal meningitis therapy. While men had consistently higher haemoglobin concentrations relative to women during the course of follow-up, changes from baseline to nadir haemoglobin values were similar in men and women (interaction term $P = 0.38$). Men experienced an average 4.0 g/dL (95% CI 3.4, 4.5 g/dL) decrease in haemoglobin, while women experienced an average 4.3 g/dL (95% CI 3.8, 4.9 g/dL) decrease in haemoglobin concentration from diagnosis to nadir values. The nadir haemoglobin concentration occurred at a median time of 14 days (IQR 8–14 days) from diagnosis.

Despite the clinically significant decline in haemoglobin levels during amphotericin induction therapy, we observed that effects were mostly transient. Among COAT participants, we observed that the median haemoglobin level had increased to 9.4 g/dL (IQR 8.1–10.8 g/dL) by 2 weeks post-induction therapy from 7.8 g/dL (IQR 6.4–9.3 g/dL) at the end of induction, and had risen to nearly 100% of baseline haemoglobin values by 12 weeks post-diagnosis (median 11.3 g/dL; IQR 9.8–12.6 g/dL). Additionally, among COAT participants who survived past the induction period, we did not observe any significant difference in rate of haemoglobin recovery by anaemia severity at baseline (interaction $P = 0.95$).

Individuals who had haemoglobin < 8.5 g/dL at diagnosis were at higher risk of death at 2 and 10 weeks (Table 2). For participants with moderate to life-threatening anaemia (grade 2–4), the hazard ratio for 2-week mortality, adjusted for sex, mental status, cryptococcal meningitis history, age, quantitative culture and ART status, was 2.7 (95% CI 1.5, 4.9; $P < 0.01$) and that for 10-week mortality was 1.8 (95% CI 1.1, 3.2; $P = 0.03$), relative to those with grade 1 or no anaemia (i.e. haemoglobin ≥ 8.5 g/dL). For participants presenting with grade

Table 2 Short-term mortality risk by haemoglobin status

		Grade 2–4 baseline haemoglobin, < 8.5 g/dL				Grade 3–4 baseline haemoglobin, < 7.5 g/dL			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	n	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
2-Week mortality	311	1.97 (1.12, 3.45)	0.02	2.69 (1.46, 4.93)	< 0.01	1.23 (0.52, 2.91)	0.64	1.41 (0.57, 3.45)	0.46
10-Week mortality	311	1.55 (0.95, 2.52)	0.08	1.82 (1.05, 3.15)	0.03	1.24 (0.62, 2.45)	0.54	1.18 (0.53, 2.62)	0.69
		Grade 2–4 nadir haemoglobin, < 8.5 g/dL				**Grade 3–4 nadir haemoglobin, < 7.5 g/dL**			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	N	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
10-Week mortality†	98	2.80 (0.82, 9.50)	0.10	2.03 (0.45, 9.12)	0.35	1.10 (0.44, 2.78)	0.83	0.70 (0.25, 1.92)	0.49

COAT, Cryptococcal Optimal ART Timing; CI, confidence interval; HR, hazard ratio.
*Comparison of patients with haemoglobin < 8.5 g/dL and those with haemoglobin ≥ 8.5 g/dL, adjusted for patient sex, age (> 50 years or ≤ 50 years), ART status at enrolment, prior history of cryptococcal meningitis, $\log_{10}$ quantitative CSF cultures/mL, and Glasgow coma scale score (< 15 or = 15)
†Only in COAT participants who survived at 2 weeks and had systematic follow-up haemoglobin measurements during the first 2 weeks.

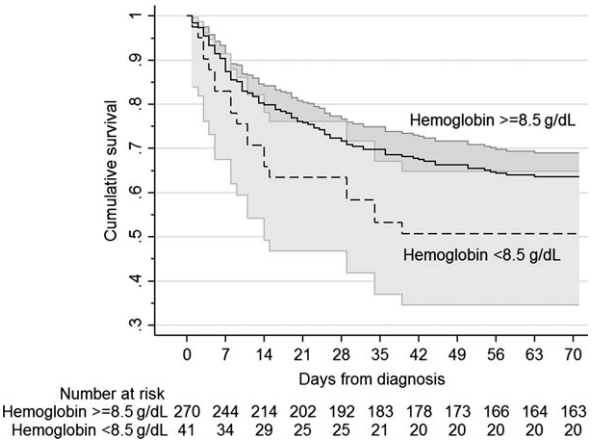

Fig. 2 Kaplan–Meier survival curves by anaemia status at cryptococcal meningitis diagnosis. HIV-infected persons with cryptococcal meningitis who had haemoglobin concentration ≤ 8.4 g/dL (≥ grade 2 adverse event severity) at diagnosis had higher 2-week mortality [hazard ratio 2.3; 95% confidence interval (CI) 1.3–4.1; $P < 0.01$] and 10-week mortality (hazard ratio 1.7; 95% CI 1.0–2.9; $P = 0.05$).

3 or 4 anaemia *vs*. those without, the adjusted hazard ratios for 2- and 10-week mortality were 1.4 (95% CI 0.6, 3.4; $P = 0.46$) and 1.2 (95% CI 0.5, 2.6; $P = 0.69$), respectively. These persons were more likely to be transfused; however, transfusion data were not systematically collected. The difference in 2- and 10-week survival between those with baseline anaemia of moderate to life-threatening severity and those with no or mild anaemia is displayed in Figure 2.

Among participants from COAT, of the 119 individuals who presented with haemoglobin ≥ 8.5 g/dL at diagnosis and survived to have further haemoglobin measurements, 66% (79 of 119) developed moderate to life-threatening anaemia (grade 2: $n = 21$; grade 3: $n = 24$; grade 4: $n = 34$) during the 2-week induction period with amphotericin therapy as shown in Table 3. The overall median nadir haemoglobin concentration among all COAT participants was 7.4 g/dL (IQR 6.2, 8.9 g/dL). The median percentage change among all COAT participants was a decrease of 31.4% (IQR −43.8, −21.7%). However, the development of anaemia during induction therapy was not associated with an increased risk of mortality at 10 weeks. The unadjusted 10-week hazard ratio for death among participants who developed grade 2–4 anaemia (haemoglobin level < 8.5 g/dL) was 2.8 (95% CI 0.8, 9.5; $P = 0.10$). The unadjusted 10-week hazard ratio for participants who developed grade 3–4 anaemia (haemoglobin ≤ 7.4 g/dL) was 1.1 (95% CI 0.4, 2.8; $P = 0.83$). Adjusting for sex, age, quantitative cultures and mental status further attenuated these results ($P = 0.19$). Among those without substantial anaemia at baseline (haemoglobin ≥ 8.5 g/dL), the difference in 10-week mortality between those who developed anaemia (grade 2–4) during the induction phase and those who did not develop anaemia is displayed in Figure 3.

Table 3 Incidence of anaemia and mortality during the 14-day amphotericin induction period among Cryptococcal Optimal ART Timing (COAT) participants with haemoglobin ≥ 8.5 g/dL at diagnosis

	Status at 2 weeks		
Anaemia AE incidence	Alive *n* (%)	Died *n* (%)	Overall *n* (%)
Haemoglobin remained ≥ 8.5 g/dL	33 (33.7)	7 (33.3)	40 (33.6)*
Grade 2 AE, haemoglobin 7.5–8.4 g/dL	18 (18.4)	3 (14.3)	21 (17.7)
Grade 3 AE, haemoglobin 6.5–7.4 g/dL	21 (21.4)	3 (14.3)	24 (20.2)
Grade 4 AE, haemoglobin < 6.5 g/dL	26 (26.5)	8 (38.1)	34 (28.6)
Total	98	21	119

AE, adverse event.
*One person died prior to receiving an additional haemoglobin measurement.

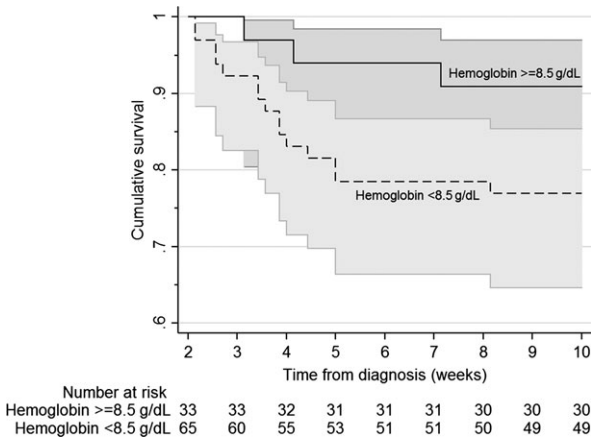

Fig. 3 Ten-week survival based on nadir haemoglobin level during amphotericin induction therapy among persons with haemoglobin ≥ 8.5 g/dL at diagnosis who survived > 14 days post-diagnosis. Participants developing moderate to life-threatening anaemia (grade 2–4 adverse event, i.e. haemoglobin < 8.5 g/dL) during amphotericin therapy had nonsignificantly higher 10-week mortality (adjusted hazard ratio 2.58; 95% confidence interval 0.64, 10.48; $P = 0.19$).

Discussion

Our analysis demonstrates that persons presenting with cryptococcal meningitis experience an acute drop in haemoglobin concentration over the 14-day induction period with amphotericin. Although this is not a new finding, our study quantifies the change from diagnosis to 12 weeks in haemoglobin concentrations in persons

undergoing amphotericin-based treatment for HIV-associated cryptococcal meningitis. Joly *et al.* [17] reported haemoglobin changes in 44 patients receiving amphotericin B deoxycholate from baseline to the end of therapy; however, changes after amphotericin were not reported. Another study carried out in South Africa reported changes from baseline to 4 weeks only [24]. Clinicians should anticipate the changes in haemoglobin concentrations in persons requiring amphotericin therapy and prepare appropriately for persons who are likely to require blood transfusion. We also investigated the association between haemoglobin values and mortality. Paradoxically, those with the most severe anaemia at baseline (haemoglobin < 7.5 g/dL) had less hazard of mortality. This group was more likely to receive prompt blood transfusions, although the timing was not systematically captured and should be explored in the future. In resource-limited settings where there is a shortage of blood products, persons at high risk for developing moderate to life-threatening anaemia should be considered as a priority for blood transfusions.

In the context of cryptococcal meningitis, other options for the management of anaemia may include shortened or interrupted courses of amphotericin. Small prospective studies have shown comparable efficacy and decreased toxicity using shorter courses of amphotericin (5–7 days). Specifically, there was no severe or life-threatening anaemia (haemoglobin ≤ 7.4 g/dL) reported in a 30-person Ugandan cohort receiving a short course of amphotericin [25,26]. Testing of whether short-course amphotericin has equivalent efficacy is ongoing with results expected in 2017 (International Standard Randomised Controlled Trials Number 45035509).

We also found that individuals with haemoglobin concentration < 8.5 g/dL at the time of cryptococcal meningitis diagnosis were at elevated risk of death at both 2 and 10 weeks post-diagnosis compared with persons who were not anemic or had mild anaemia. A number of previous studies among HIV-infected individuals have shown that anaemia is independently associated with mortality [2–6]. In fact, in persons with AIDS, the risk of death increases as haemoglobin levels decline [27]. Therefore, it is not surprising that individuals who present with moderate to life-threatening anaemia at cryptococcal meningitis diagnosis are at higher risk of death. A similar observation was noted in South Africa, where persons with HIV-associated cryptococcal meningitis and a baseline haemoglobin concentration < 7.5 g/dL were at threefold higher odds of death at 10 weeks [21]. Although there was a significant decline in haemoglobin levels during the 14 days of treatment with amphotericin, we noted that the median haemoglobin level had increased to 9.5 g/dL by 4 weeks post-diagnosis from 8.1 g/dL at the end of induction. The haemoglobin values rose further to 90% of their original (pretreatment) values at 12 weeks post-diagnosis. This is similar to findings from a previous study where change in median haemoglobin levels was reported from baseline to 4 weeks only. Values at baseline, week 2, and week 4 were 10.4, 7.7, and 8.5 g/dL, respectively [24]. While transfusion data were not available for these patients, future studies should assess whether transfusions at the onset of amphotericin administration in persons presenting with grade 3–4 anaemia (haemoglobin < 7.5 g/dL) can impact survival.

The anaemia–mortality association seems to be driven by factors present at diagnosis, rather than treatment toxicity itself. Having anaemia at baseline is probably a marker of a combination of more advanced HIV disease, more disseminated opportunistic infections (OIs), and in some patients an undiagnosed OI, and may explain the increase in mortality seen in individuals presenting with a baseline haemoglobin level < 8.5 mg/dL. We believe that persons at high risk to develop life-threatening anaemia (i.e. persons with baseline anaemia, often female) should be given priority when considering additional interventions.

There were several limitations to our study. There were only a few participants who presented with grade 3 and 4 anaemia and the study may have been underpowered to detect a statistical difference in mortality. Additionally, some participants received blood transfusions when haemoglobin levels dropped below 6.5 g/dL, although this was not universal given the limited availability of blood products. Unfortunately, data on blood transfusions were not comprehensively captured.

In summary, we have found that this African cohort of HIV-infected persons with cryptococcal meningitis experienced a drop of 3.1 g/dL over the 14-day amphotericin-based induction period. Once amphotericin therapy was completed, haemoglobin levels rebounded to 90% of baseline haemoglobin values within 12 weeks post-diagnosis. Ultimately, the development of acute anaemia during the 14-day induction period with amphotericin was not found to affect 10-week mortality. Importantly, anaemia even of moderate severity at the time of cryptococcal meningitis diagnosis can be used as a prognostic indicator of mortality. We believe that our results can be generalized to persons with AIDS receiving amphotericin for systemic fungal infections other than cryptococcosis. If the efficacy of shorter durations (5–7 days) of amphotericin induction therapy is confirmed in larger studies, shorter courses of amphotericin should be considered for persons at high risk (i.e. persons with baseline anaemia,

often female) of developing severe to life-threatening anaemia while on amphotericin.

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