Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries

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In 2018, WHO issued guidelines for the diagnosis, prevention, and management of HIV-related cryptococcal disease. Two strategies are recommended to reduce the high mortality associated with HIV-related cryptococcal meningitis in low-income and middle-income countries (LMICs): optimised combination therapies for confirmed meningitis cases and cryptococcal antigen screening programmes for ambulatory people living with HIV who access care. WHO's preferred therapy for the treatment of HIV-related cryptococcal meningitis in LMICs is 1 week of amphotericin B plus flucytosine, and the alternative therapy is 2 weeks of fluconazole plus flucytosine. In the ACTA trial, 1-week (short course) amphotericin B plus flucytosine resulted in a 10-week mortality of 24% (95% CI –16 to 32) and 2 weeks of fluconazole and flucytosine resulted in a 10-week mortality of 35% (95% CI –29 to 41). However, with widely used fluconazole monotherapy, mortality because of HIV-related cryptococcal meningitis is approximately 70% in many African LMIC settings. Therefore, the potential to transform the management of HIV-related cryptococcal meningitis in resource-limited settings is substantial. Sustainable access to essential medicines, including flucytosine and amphotericin B, in LMICs is paramount and the focus of this Personal View.

Introduction

Evidence from randomised controlled trials supports the urgent need for the addition of flucytosine to regimens for safe and effective treatment of cryptococcal meningitis for people living with advanced HIV disease.[1] HIV-related cryptococcal meningitis remains the commonest cause of meningitis in many low-income and middle-income countries (LMICs).[1–3] Effective treatments for HIV-related cryptococcal meningitis in resource-limited settings consist of flucytosine with fluconazole, conventional amphotericin B deoxycholate, or liposomal amphotericin B. However, flucytosine is unavailable in LMICs and unregistered in any African country, despite it being an old, off-patent, and easy to manufacture medicine.[2,3] We present the latest burden of disease and clinical trial data that underline the need for urgent action to ensure access to flucytosine and amphotericin B in LMICs, and we highlight the publication of new WHO guidelines about HIV-related cryptococcal disease.[4] We review the good safety profile of flucytosine for the treatment of HIV-related cryptococcal meningitis, outline the barriers around access to standard formulations of flucytosine and standard and liposomal formulations of amphotericin B, and highlight the need for better adapted modified-release formulations of flucytosine.

Burden of cryptococcal meningitis and factors associated with high mortality

Published data have shown that cryptococcal meningitis causes 15–20% of AIDS-related mortality.[5] Cryptococcal meningitis is caused by the fungus *Cryptococcus neoformans*. Mortality from cryptococcal meningitis in resource-limited settings is approximately 70%, with most centres in LMICs having no access to cryptococcal antigen lateral flow assay tests and essential medicines, including flucytosine.[5] Cryptococcal antigen lateral flow assays have revolutionised the diagnosis of cryptococcal disease, providing highly sensitive and specific testing of blood and cerebrospinal fluid samples. There are an estimated 223 100 cases of cryptococcal meningitis annually, with approximately three-quarters occurring in Africa.[5] In sub-Saharan Africa alone there are an estimated 135 900 deaths annually, with most people living with HIV receiving suboptimal fluconazole monotherapy, if they are diagnosed.[5] Importantly, unlike in high-income countries, there is no sign of a decrease in the number of cryptococcal meningitis cases in most LMICs, despite the roll-out of antiretroviral therapy (ART) and the UNAIDS/WHO 90-90-90 continuum of HIV care targets.[1,6–9] In fact, half to three-quarters of patients presenting with cryptococcal meningitis in LMICs have received ART previously.[1,6–10]

Trial data: treatment and prevention of cryptococcal meningitis

To reduce the unacceptably high mortality associated with cryptococcal meningitis, two strategies have emerged: new combination treatments that are more effective and safe to administer in resource-limited settings,[1,11] and cryptococcal antigen screening programmes that can

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detect cases earlier or prevent the development of cryptococcal meningitis with pre-emptive antifungal treatment of people with advanced HIV (CD4 count of ≤200 cells per µL) who screen cryptococcal antigen -positive[4,12,13] (figure 1).

In the acute care setting, for cases of confirmed cryptococcal meningitis, the focus of recent research has been on finding alternative treatments to the previous gold standard of 2 weeks of amphotericin B and flucytosine, which is either unavailable in the case of flucytosine or unsafe to use in resource-limited settings without intensive patient and laboratory monitoring, which can be difficult to obtain. On one hand, administration is intravenous and requires hospitalisation and careful laboratory monitoring and management. On the other hand, the mortality observed in routine care in resource-limited settings where fluconazole therapy is more easily available and commonly prescribed is approximately 70%.[5] The results of the ACTA trial showed that short course (1-week) amphotericin B and flucytosine could decrease 10-week mortality to 24% (95% CI –16 to 32).[1] They also showed that 2 weeks of flucytosine and fluconazole performed well and reduced mortality to 35% (figure 2). Mortality in the 2-week amphotericin B groups was 39·7% (95% CI –33·5 to 46·2) at 10 weeks.[1] Two alternative combination induction therapy options for the management of HIV-related cryptococcal meningitis in resource-limited settings have thus emerged: 1-week amphotericin B and flucytosine; and an easily implementable oral combination therapy of 2 weeks of flucytosine and fluconazole. Both combination treatment strategies could enable people with HIV to be discharged from hospitals before the end of the 2-week induction treatment period, reducing hospital-care costs substantially. Lastly, the ACTA trial showed that, compared with fluconazole, flucytosine is a more effective companion drug for induction therapy[1] (figure 3). This finding is important, as in many LMIC settings where flucytosine is unavailable but amphotericin B can be administered safely, amphotericin B is given in combination with fluconazole for the treatment of HIV-related cryptococcal meningitis.[1]

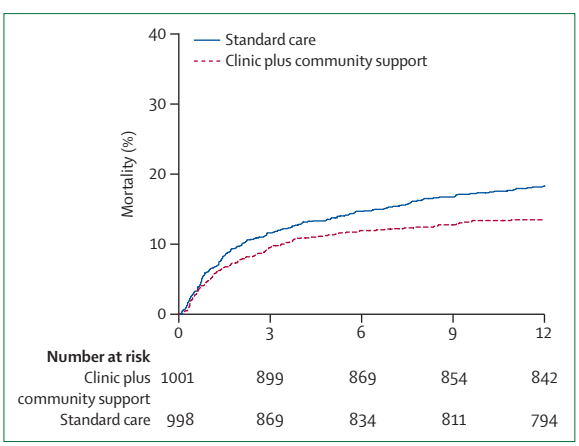

Figure 1: **All-cause mortality in the clinical plus community support and standard care groups. From the REMSTART trial[13]**

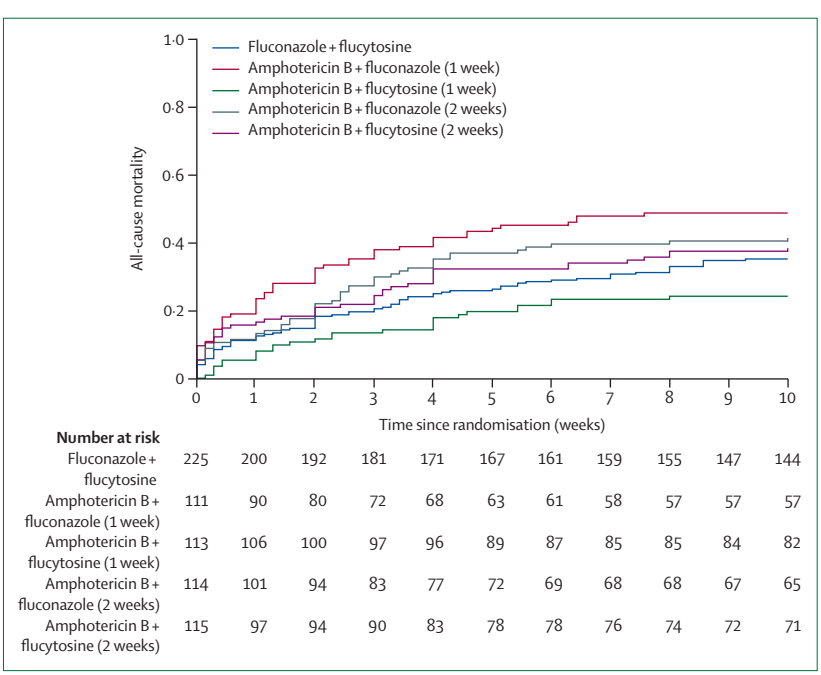

Figure 2: **Cumulative incidence of all-cause mortality by week 10 according to the ACTA treatment strategies[1]**
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Programmes to pre-emptively treat people living with advanced HIV disease who are asymptomatic but with detectable cryptococcal antigen in blood also offer the opportunity to reduce cryptococcal-related mortality. The detection of cryptococcal antigen weeks to months before the development of cryptococcal meningitis using cryptococcal antigen lateral flow assays underlies the rationale behind cryptococcal antigen screen-and-treat programmes, which are now in the national guidelines of 24 countries.[12] The REMSTART trial,[13] a multicentre trial that took place in Zambia and Tanzania, was the first to show a 28% reduction in mortality when cryptococcal antigen screening was combined with adherence support counselling compared to standard clinic-based care alone for people with advanced HIV disease. However, despite pre-emptive therapy with 2 weeks of fluconazole, the mortality of cryptococcal antigen-positive people with HIV remained two to three times higher than the mortality of people with HIV screening cryptococcal antigen negative.[13] Additionally, there is consistent and increasing evidence suggesting that as many as 40% of people with advanced HIV disease who screen cryptococcal antigen-positive have subclinical meningitis, irrespective of symptoms.[14–17] Flucytosine might therefore prove important for the optimal treatment of cryptococcal antigen-positive people with HIV who are likely to benefit from more aggressive pre-emptive treatment. 2 weeks of fluconazole and flucytosine is an easily implementable and safe oral induction treatment option for people with a high positive titre of cryptococcal antigen and HIV presenting

to primary care centres where intravenous administration of medicines is not generally feasible. The presence of high cryptococcal antigen titres correlates with the presence of cryptoccocal meningitis and can be detected with new, second-generation lateral flow assays.[14,18]

Flucytosine safety profile

Evidence from pooled cohorts of over 1000 patients treated in resource-limited settings in Africa and Asia indicates that, at recommended doses (100 mg/kg per day for 2 weeks), oral flucytosine can be administered safely with conventional amphotericin B or fluconazole to patients with HIV.[2,19] Furthermore, in people living with HIV, flucytosine drug-level monitoring is not required.[1,2,20] Previously, there have been concerns about the safety of flucytosine relating to early studies that used a high dose of the drug for more than 2 weeks, or in other populations such as premature infants and patients with renal failure in critical care. Although the safety profile is much improved when used at recommended doses and durations, some routine laboratory monitoring (ie, baseline and day 7 full blood count and creatinine) is still advisable if possible, with flucytosine dose adjustments in case of neutropenia and renal impairment.

Barriers to flucytosine and amphotericin B access in LMICs

The standard formulation of flucytosine is a good example of a market failure in resource-limited settings where the need is greatest.[2,3] Specific barriers to access include: flucytosine not being listed in countries' national essential medicine lists (despite being in WHO's essential medicine list since 2013), scarcity of in-country registration, high cost, and shortage of generic manufacturers interested in developing the drug. Flucytosine is unregistered in any African country. In South America flucytosine is registered in Brazil and Argentina, but only available in Colombia and French Guiana. Although, there are several manufacturers of generic flucytosine that have been approved by the regulatory authority, none are supplying flucytosine in countries that need it the most. Ministries of health, national drug regulatory authorities, international funders, and drug manufacturers should collaborate to ensure that flucytosine is listed in national formularies, registration is expedited (through WHO's collaborative registration mechanism when possible), and flucytosine's market failure is addressed. Additionally, there is low and unpredictable demand for flucytosine, fluconazole, and amphotericin B from countries and a scarcity of financing for a disease that causes up to 20% HIV-related mortality. Increased awareness of the safety and efficacy of a 1-week intravenous-based therapy or a 2-week oral course of fluconazole and flucytosine is expected to substantially increase demand for and uptake of flucytosine.

Amphotericin B is the most rapidly acting medicine against *C neoformans* but requires intravenous administration and careful monitoring of blood counts and renal

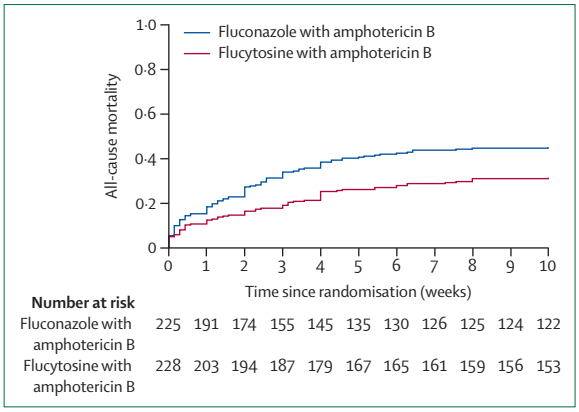

Figure 3: **Cumulative incidence of all-cause mortality by week 10 according to amphotericin B partner treatment (fluconazole or flucytosine) within the ACTA trial[1]**
Reproduced from Molloy and colleagues,[1] by permission of Massachusetts Medical Society.

function to manage common side-effects such as anaemia and renal impairment.[3,19] WHO outlines a minimum package for the prevention, monitoring, and management of toxicity to minimise serious amphotericin B-related side-effects.[4] The 1-week amphotericin B combination strategy had the added benefit of a good safety profile with less laboratory monitoring required compared with a the 2-week course.[1,19] Indeed, anaemia and renal impairment are more common in the second week of amphotericin B therapy.[19] Barriers to amphotericin B access in LMICs include: high cost, scarcity of widely accessible training programmes for safe amphotericin B administration, and uncoordinated funding, procurement, and drug distribution.[3] Liposomal amphotericin B has similar efficacy and superior tolerability compared with amphotericin B deoxycholate, and in combination with high-dose fluconazole it has been shown to be effective for the treatment of cryptococcal meningitis.[21–23] A single dose of liposomal amphotericin B (10 mg/kg) combined with fluconazole and flucytosine is being evaluated in an ongoing phase 3 clinical endpoint trial (ISRCTN 10248064) High cost and scarcity of registration remain the biggest barriers to less toxic liposomal amphotericin B formulations being used in resource-limited settings.[3]

Modified-release formulations of flucytosine

The dosing schedule for flucytosine (100 mg/kg per day in four divided doses) is problematic, particularly for resource-limited settings where health-care facilities are overcrowded and routine care staff are overburdened. Additionally, most cryptococcal meningitis patients have a reduced level of consciousness, with standard formulations being crushed and given by nasogastric intubation. The development of modified-release formulations of flucytosine administered once or twice daily, better adapted to effective administration by nasogastric intubation and dose adjustment, is a priority for such

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Panel: **Actions to increase access to safe and effective treatment for cryptococcal meningitis**

- Incorporate 2018 WHO guidance on HIV-related cryptococcal disease and management of advanced HIV into countries' national guidelines, supported by national dissemination and training
- Expedite registration of existing flucytosine formulations in high burden low-income and middle-income countries (LMICs) using WHO's collaborative procedure for accelerated registration as one of the methods
- Include flucytosine, conventional deoxycholate, and liposomal formulations of amphotericin B in the essential medicines lists of LMICs
- Ensure capacity for sustainable supply of cryptococcal antigen diagnostic tests, flucytosine, amphotericin B deoxycholate, and liposomal amphotericin B to meet country demands as they implement the WHO guidelines and scale-up
- LMICs to work with partners to quantify amounts of cryptococcal antigen tests and essential medicines needed and include these estimates in Global Fund applications and US Centers for Disease Control and Prevention and President's Emergency Plan for AIDS Relief agreements
- Prioritise the development of a modified-release formulation of flucytosine

patients. However, the development of modified-release formulations should not detract from registration and increased access to standard formulations of flucytosine that are available in LMICs.

New WHO guidelines for the management of HIV-related cryptococcal disease

New WHO guidelines in 2018 recommend both 1 week of amphotericin B with flucytosine and 2 weeks of flucytosine and fluconazole as induction regimens for cryptococcal meningitis.[4] Cryptococcal antigen screening for all adults and adolescents with advanced HIV disease, and pre-emptive therapy if they are cryptococcal antigen-positive, is also recommended.[4] These recommendations are expected to become the new gold standard treatments and standard of care for resource-limited settings.[4]

Conclusion

The reduction of persistent and unacceptable high mortality of people with advanced HIV disease, affecting approximately a third of patients with HIV in LMICs, is an important focus in keeping with WHO's 2017 guidelines on managing advanced HIV.[24] It is paramount to tackle the high mortality of HIV-related cryptococcal meningitis and improve access to flucytosine and conventional deoxycholate and liposomal formulations of amphotericin B in LMICs (panel).

Contributors
The idea for this Personal View was conceived during a meeting of the cryptococcal meningitis action group (cryptoMAG). AL wrote the first draft of the manuscript and then incorporated key input from all the authors. All authors reviewed the manuscript.

Declaration of interests
NG received personal fees from Astellas Pharma and non-financial support from MSD outside the submitted work. JD received personal fees from Viamet Pharmaceuticals outside the submitted work. JNJ received grants from Gilead Sciences Europe outside the submitted work. TB received grants and personal fees from Gilead Sciences Inc outside the submitted work. RH received grants from Medical Research Council and Wellcome Trust during the conduct of the study. TSH received grants from Medical Research Council (UK), ANRS (France), Gilead Sciences, and Immunomycologics and personal fees from Viamet, Gilead Sciences, and Pfizer during the conduct of the work. OL received personal fees from MSD, Astellas Pharma, Pfizer, and Gilead outside the submitted work. DD and family hold founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. DD acts or has recently been a consultant to Scynexis, Cidara, Quintiles, Pulmatrix, Pulmocide, Zambon, Roivant, and Fujifilm. In the past 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, Mylan, and Pfizer. He is a member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology, Infectious Diseases Aspergillosis Guidelines group, and the British Society for Medical Mycology Standards of Care committee. DD has a patent licenced for Assays for Fungal Infection. All other authors declare no competing interests.

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