Reply to Rajasingham and Boulware

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Dear Editor:

In 2015 there was widespread outrage after the New York Times publicized the 5000% increase in the price of Pyrimethamine (Daraprim) by Turing Pharmaceuticals; a drug used primarily to treat toxoplasmosis in patients with advanced HIV disease[1]. Pyrimethamine was not the only previously low-cost generic medication for an HIV-related opportunistic infection subject to such predatory pricing; in 2016 Merry and Boulware reported the dramatic impact a similarly explosive increase in the price of flucytosine (5-FC) was having on the cost of treating cryptococcal meningitis in the U.S.[2]. The cost of a two-week course of flucytosine, a sixty year old and easy to manufacture molecule[3], had risen to nearly $30,000, 9000% higher than the equivalent treatment in the U.K.[2]. It is therefore encouraging to see the marked decline in flucytosine pricing in the U.S. following the FDA's approval of three new generic formulations, as reported by Rajasingham and Boulware in this issue of the journal[4]. Although, as with Pyrimethamine[5], flucytosine remains expensive in the U.S., this is clearly a step in the right direction. And very timely, given new clinical trial evidence clearly showing the critical importance of flucytosine as a component of combination treatment for HIV-associated cryptococcal meningitis[6]. In the recent Advancing Cryptococcal Treatment for Africa (ACTA) trial, flucytosine was significantly superior to high dose fluconazole as the partner drug for amphotericin B, leading to improved survival at ten weeks (HR 0.62, 95% confidence interval 0.45-0.84)[6].

While improved flucytosine pricing for U.S. patients is a very positive development, the bulk of the burden of cryptococcal disease lies in low and middle income countries (LMICs); primarily sub-Saharan Africa[7]. Cryptococcal meningitis causes an estimated 135,900 deaths annually in Africa[7], approximately 15% of all HIV-related deaths, and the number of cases remains high despite the expansion of antiretroviral treatment (ART) programs[8, 9]. Increasing numbers of patients on long-term ART interrupting, stopping, or failing therapy are offsetting any decline in the numbers of

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patients presenting for the first time with advanced HIV-disease[8], and in many settings the majority of cryptococcal meningitis patients are now ART-experienced[8, 10]. A major contributor to the high death rates due to cryptococcal meningitis in LMICs is lack of access to effective treatments. Many patients are treated with fluconazole monotherapy, with use of amphotericin B based therapies limited by cost and the difficulties of managing daily intravenous infusions and drug related toxicities in resource-constrained healthcare facilities. It was thus a major advance when the ACTA trial demonstrated that both an abbreviated seven-day course of amphotericin B deoxycholate plus flucytosine, and an all-oral combination of high dose fluconazole plus flucytosine were non-inferior to conventional 2-week amphotericin B deoxycholate based treatments[6], highlighting the importance of flucytosine access in LMICs[11].

In their article, Rajasingham and Boulware calculate that universal implementation of cryptococcal antigen (CrAg) screening for all individuals with AIDS in the U.S., with pre-emptive treatment for those who have detectable cryptococcal antigenemia to prevent fulminant meningitis, could lead to considerable cost savings[4]. The CrAg screening strategy is recommended by the WHO[12] based on evidence showing that (a) asymptomatic cryptococcal antigenemia is common among individuals initiating ART with CD4 counts (~6.5% of patients with CD4 < 100 cells/μL)[13], (b) cryptococcal antigenemia is highly predictive of subsequent cryptococcal meningitis[14], and (c) high dose fluconazole treatment in CrAg-positive patients substantially reduces the incidence of cryptococcal meningitis (from 21.4% to 5.7% in a recent meta-analysis)[15]. CrAg screening has now been adopted in several African countries[16], but as Rajasingham and Boulware point out, current treatment strategies for patients with asymptomatic cryptococcal antigenemia based on high dose oral fluconazole (800-1200mg per day) alone are suboptimal. Mortality among asymptomatic CrAg-positive patients treated with high dose fluconazole in LMICs remains over two-fold higher than in CrAg-negative patients with similar CD4 counts[15, 17, 18], in part due to the high frequency of

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undiagnosed cryptococcal meningitis in these patients[17, 19]. Flucytosine may also have an important role here. Given the proven efficacy of the oral fluconazole and flucytosine combination for treating cryptococcal meningitis in the ACTA Trial, the oral combination would certainly seem like a rational therapeutic option for CrAg-positive patients; particularly in LMIC contexts where it is not feasible to perform lumbar punctures (LPs) in all CrAg-positive patients to determine if there is central nervous system (CNS) involvement. In such settings, the fluconazole plus flucytosine combination could be given to all asymptomatic CrAg-positive patients, in the knowledge that it would be efficacious even in those with undiagnosed meningitis. Studies of the efficacy and cost effectiveness of this approach are urgently needed and planned. However, in resource-rich settings, most experts would still recommend fully investigating all CrAg-positive patients with lumbar puncture, and Amphotericin B-based treatment, usually the liposomal formulation, plus flucytosine for those found to have cryptococcal meningitis on CSF investigation as per current national guidelines[20, 21, 22]. Oral fluconazole and flucytosine could still be given to individuals without CNS involvement, although the benefit of adding flucytosine to fluconazole monotherapy in this group is currently unknown.

A potential alternative treatment strategy for asymptomatic CrAg-positive individuals identified at screening is adding single high-dose liposomal amphotericin B (10mg/kg) to the currently recommended high dose fluconazole. We have recently demonstrated in the phase II Ambition-cm trial that this combination leads to non-inferior CSF fungal clearance compared to fourteen days of standard dose liposomal amphotericin B (3mg/kg) plus high dose fluconazole in patients with HIV-associated cryptococcal meningitis[23]; and Rajasingham and Boulware suggest that as an outpatient treatment for CrAg-positive individuals in the U.S. this could be economical[4]. This strategy does need rigorous study prior to implementation. As with the fluconazole and flucytosine oral combination, in well-resourced settings where diagnostic LPs are readily available, clinicians will

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be reluctant to use this abbreviated liposomal amphotericin treatment course in CrAg-positive individuals with CNS involvement detected at LP in the absence of robust trial data; and conversely a dose of liposomal amphotericin may not be necessary in CrAg-positive individuals without CNS involvement. In resource limited settings where LPs are not so easily accessible, a blanket approach using single high doses of liposomal amphotericin B in addition to high dose fluconazole may well have merit, although careful study of the feasibility, clinical efficacy, and cost-effectiveness of the strategy are needed. We are currently testing single high-dose liposomal amphotericin B (10mg/kg) treatment for patients with cryptococcal meningitis in the ongoing phase III Ambition-cm study (ISRCTN72509687); but notably we are using this with an oral combination of fluconazole *plus* flucytosine. This change from the regimen used in the phase II trial was made based on the ACTA trial data. Studying whether the duration of amphotericin B deoxycholate could be reduced from fourteen to seven days, the ACTA investigators found that when given with flucytosine, short course amphotericin performed well, resulting in the lowest 10 week mortality of all treatment arms (24%, 95% CI 16-32). But short course amphotericin B given with fluconazole was the least effective treatment arm, with a 10 week mortality of 49% (95% CI 39-58)[6], suggesting that the robust antifungal efficacy of flucytosine is required if the duration of the amphotericin B deoxycholate component of treatment is to be reduced. Whether this is also the case with liposomal amphotericin, or in asymptomatic CrAg-positive individuals including those with sub-clinical cryptococcal meningitis, needs to be determined.

Overall, the arrival of competition in the generic market for flucytosine can only be a good thing for patients with advanced HIV-disease in the U.S. and globally. After many years of relative neglect[24-26], cryptococcal meningitis is now gaining some of the attention it deserves from funders[27] and policy makers[12]. The World Health Organization (WHO) has led a renewed focus on advanced HIV-disease, releasing important new guidelines on both advanced HIV-disease[26], and cryptococcal

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meningitis prevention and treatment[12]. Considerable advocacy efforts driven by the cryptoMAG consortium[11], Médecins Sans Frontières[29], and others, are already underway to increase global access to cryptococcal meningitis treatments, in particular flucytosine[11]. In the Ambition-cm trial flucytosine is being procured at US$1.30 per 500mg tablet (about US$180 per 2 week course). Further price reductions are needed and are possible. Recent successes of the advocacy work around HIV-associated cryptococcal meningitis[11, 29] include the WHO prequalification of liposomal amphotericin B (AmBisome) in June 2018[30]; the addition of cryptococcal meningitis to the U.S. Food and Drug Administration's priority review voucher scheme to encourage drug development in August 2018[31]; and the expansion of Gilead's preferential AmBisome pricing program for visceral leishmaniasis to include cryptococcal meningitis in September 2018[32]. We now have the opportunity to build on these recent advances to refine strategies for treatment and prevention of cryptococcal meningitis through robust clinical trials, and continue advocacy work to ensure that these interventions are made available to the individuals with advanced HIV disease who need them.

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Conflict of Interest Statement

Dr. Harrison reports grants and personal fees from Gilead Sciences, personal fees from Pfizer, and personal fees from Viamet, during the conduct of the study. Dr. Jarvis reports grants from Gilead, outside the submitted work.

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