Single-Dose Amphotericin B for Cryptococcal Meningitis

TO THE EDITOR: Jarvis et al. (March 24 issue)[1] showed that a regimen that included a single dose of liposomal amphotericin B (10 mg per kilogram of body weight) followed by 14 days of treatment with flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) was noninferior to the current treatment recommended by the World Health Organization (WHO) for cryptococcal meningoencephalitis, with fewer adverse events. The need for better treatment regimens for cryptococcosis is urgent, because the estimated global rate of death associated with the condition is 181,000 cases per year.[2] The trial results are consistent with the pharmacodynamic properties of amphotericin B and could have a substantial effect on clinical practice. We believe that the main issue here is not whether liposomal amphotericin B works in single-dose regimens but rather whether it can be made available (and affordable) in places where it is needed most, including Latin America, Africa, and Southeast Asia. Liposomal amphotericin B — not to mention 5-fluorocytosine — is scarce in most of these places. Only four countries in sub-Saharan Africa have access to liposomal amphotericin B,[3] and it is unavailable in most public health systems in Latin America.[4] It is time for scientists, politicians, and members of industry to work together to make this treatment available for the benefit of global public health.

Diego R. Falci, M.D., Ph.D.

Pontificia Universidade Católica do Rio Grande do Sul
Porto Alegre, Brazil

Alessandro C. Pasqualotto, M.D., Ph.D.

Santa Casa de Misericordia de Porto Alegre
Porto Alegre, Brazil
pasqualotto@santacasa.org.br

Dr. Falci reports receiving research support and lecture and consulting fees from United Medical, MSD, and Pfizer, and Dr. Pasqualotto, receiving grant support from Gilead and lecture fees from United Medical. No other potential conflict of interest relevant to this letter was reported.

1. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. N Engl J Med 2022;386:1109-20.
2. Rajasingham R, Smith RM, Park BJ, et al. Global burden of

disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 2017;17:873-81.
3. Driemeyer C, Falci DR, Oladele RO, et al. The current state of clinical mycology in Africa: a European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey. Lancet Microbe 2022;3(6):e464-e470.
4. Falci DR, Pasqualotto AC. Clinical mycology in Latin America and the Caribbean: a snapshot of diagnostic and therapeutic capabilities. Mycoses 2019;62:368-73.

DOI: 10.1056/NEJMc2206274

THE AUTHORS REPLY: We agree with Falci and Pasqualotto that there is an urgent need to improve access to antifungal treatments for HIV-associated cryptococcal meningitis. The findings reported from the Ambition trial can galvanize this process. The trial that preceded it, Advancing Cryptococcal Meningitis Treatment,[1] showed the superiority of flucytosine and led to a revision of WHO guidelines,[1] which in turn resulted in increased demand, additional manufacturers, and substantial price reductions. In South Africa, the uptake of flucytosine has been associated with a dramatic improvement in outcomes of routine care.[2] After publication of the Ambition trial, the WHO issued rapid guidance recommending the single high-dose liposomal amphotericin regimen,[3] and guideline changes have already taken place in countries with a high burden of disease, including Botswana, Malawi, and Uganda. The partnership between Unitaid and the Clinton Health Access Initiative in providing antifungal agents in these countries has led to the provision of the Ambition regimen in routine care. Long-term access is crucial; the Global Fund and the President's Emergency Plan for AIDS Relief, or PEPFAR, plan to provide funding for key antifungal drugs, and Gilead Sciences has committed to expanded-access pricing for AmBisome. Ongoing implementation work and widespread access to liposomal amphotericin and flucytosine will be critical to reducing global mortality from cryptococcal meningitis.[4]

David S. Lawrence, M.B., Ch.B.

London School of Hygiene and Tropical Medicine
London, United Kingdom

Thomas S. Harrison, M.D.

St George's University London
London, United Kingdom

Joseph N. Jarvis, M.B., B.S., Ph.D.

London School of Hygiene and Tropical Medicine
London, United Kingdom
joseph.jarvis@lshtm.ac.uk

Since publication of their article, the authors report no further potential conflict of interest.

1. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med 2018;378:1004-17.
2. Mashau RC, Meiring ST, Quan VC, et al. Outcomes of flucytosine-containing combination treatment for cryptococcal meningitis in a South African national access programme: a cross-sectional observational study. Lancet Infect Dis 2022 June 21 (Epub ahead of print).
3. World Health Organization. New guidelines from WHO recommend a simpler, safer treatment for cryptococcal disease in people living with HIV. April 20, 2022 (https://www.who.int/news/item/20-04-2022-rapid-advice-new-guidelines-for-simpler-safer-treatment-for-cryptococcal-disease-in-plhiv).
4. Shroufi A, Chiller T, Jordan A, et al. Ending deaths from HIV-related cryptococcal meningitis by 2030. Lancet Infect Dis 2021;21:16-8.

DOI: 10.1056/NEJMc2206274