Clinical Infectious Diseases

BRIEF REPORT

Access to Medicines for Treating People With Cryptococcal Meningitis

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Cryptococcal meningitis accounts for 1 in 5 AIDS-related deaths globally. World Health Organization guidelines strongly recommend a single high dose of liposomal amphotericin B as part of preferred treatment, but this drug remains unaffordable in most low- and middle-income countries. A proactive approach is needed from manufacturers and other stakeholders to improve access.

Keywords. access; cryptococcal meningitis; HIV/AIDS; liposomal amphotericin B; mortality.

The decline in human immunodeficiency virus (HIV)–associated deaths has stagnated, and there is a growing appreciation that advanced HIV disease is a persistent challenge that requires targeted attention. Cryptococcal meningitis (CM) remains a leading cause of HIV-associated mortality [1]. An updated review of the global burden of cryptococcal disease shows little change over the past decade. From 2020 estimates, there are 179 000 cases of cryptococcal antigenemia (infection) globally in 2020 and 152 000 cases of CM, resulting in 112 000 cryptococcal-related deaths. There has been a reduction in the estimated absolute global burden of HIV-associated CM compared to estimates from 2014, likely due to expanded coverage of antiretroviral therapy; however, cryptococcal disease still accounts for 1 in 5 AIDS-related deaths, similar to previous estimates [1, 2].

The new guidelines on clinical management of CM issued by the World Health Organization (WHO) in June 2022 strongly recommend a single high dose of liposomal amphotericin B with 2 weeks of flucytosine and fluconazole as the preferred treatment [3]. This recommendation was made following a multicountry trial showing this regimen is at least as effective as the standard of care, with better safety and fewer monitoring demands. The favorable safety profile of the single-dose liposomal amphotericin B–containing regimen has a lower risk of anemia and hypokalemia, reducing the intensity of monitoring and the need to manage drug-related toxicity [4]. The single high-dose regimen was also preferred by providers because it is less time consuming to prepare and may allow for faster hospital discharge [5].

Liposomal amphotericin B is a preferred drug for the management of a number of coinfections that are common among people with HIV. In the last 2 years, WHO has released guidelines for the management of disseminated histoplasmosis [6] and visceral leishmaniasis [7] in people with HIV, and both of these guidelines recommend liposomal amphotericin B as part of a preferred treatment regimen. However, despite having received regulatory approval in 1997 [8], and being off patent since 2016 in the United States (US) [9], the drug remains unaffordable and unavailable in public healthcare systems in most low- and middle-income countries (LMICs).

In 2018, the brand manufacturer, Gilead, committed with Unitaid to a preferential price of US$16.25 per vial for 116 countries but, as of the end of 2021, less than half of eligible countries had been able to procure it at this preferential price. Those that have been able to access this preferential price have often faced long lead times, supply shortages, and procurement delays. Meanwhile, Gilead has recently indicated that it intends to increase this preferential price by almost 25% to US$19–$20 per vial in early 2023.

In South Africa, a country with a high burden of HIV and consequent mortality due to CM, liposomal amphotericin B is still priced as high as US$205 per vial or US$2500 per person [10] in the private market while not even available in the public sector. In India, it is available only in the private market via Gilead's distributor, Viatris, at a price of US$69 per vial. In Brazil, where Gilead's preferential pricing is applicable for the treatment of leishmaniasis, but not for CM, the price reaches US$373 per vial or approximately US$4500 to treat 1 person [11]. Access to this preferential pricing is limited mainly to CM.

Figure 1 illustrates the disparity of price of a 50-mg vial of liposomal amphotericin B compared to country wealth (as measured by gross national income): LMICs with a high burden of HIV—including Brazil, Peru, South Africa, and Thailand—are paying far more than high-income countries in Europe such as Belgium, France, Luxembourg, Spain, and Switzerland.

A new pathway for more sustainable access is opening, with some generic manufacturers developing liposomal amphotericin B, and 1 generic already approved by the US Food and Drug Administration (FDA) (16 December 2021). Unitaid has issued an expression of interest [13] to offer support in overcoming barriers to market entry, in an effort to ensure that the successes

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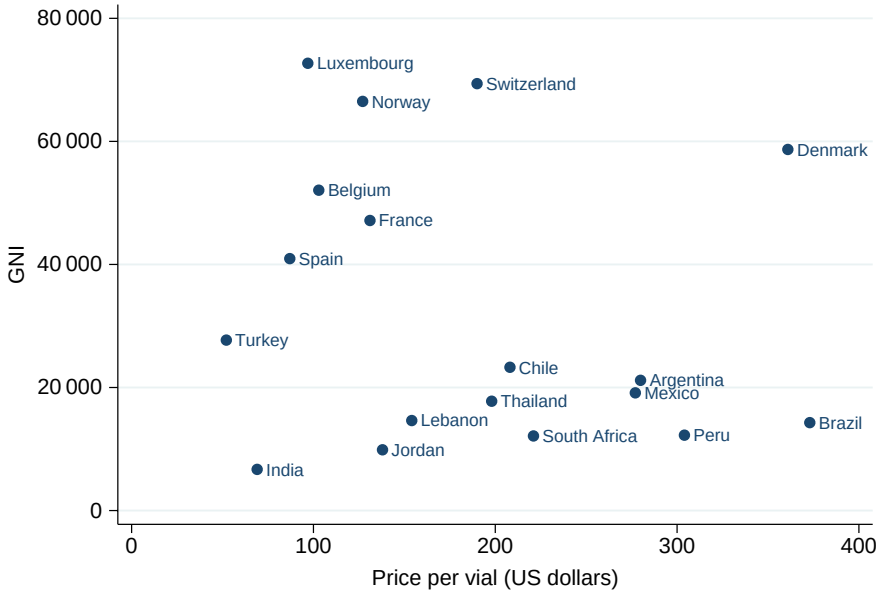

Figure 1. Correlation between the price of liposomal amphotericin B and gross national income (GNI). Full pricing table and sources are shown in Supplementary Table 1. Data on GNI (United States [US] dollars) were obtained from the United Nations Development Programme [12].

seen in these landmark clinical trials translate into broader access. While demand to date has been low, this could change with the adoption of the new WHO guidelines for managing cryptococcal disease and improved access conditions.

While the lack of patent barrier means generics manufacturers are free to enter the global market, they are more likely to target commercially lucrative markets of high-income or upper-middle-income countries, where the originator drug is sold at excessively high prices. In the US, for example, where liposomal amphotericin B from Gilead sells at more than US $300 per vial, the market is worth approximately US$136 million annually [14].

Generic companies must allocate a portion of their manufacturing capacity to supplying LMICs at an affordable price, many of which still do not have adequate access to this lifesaving medicine and cannot provide the gold standard of treatment for people with CM.

Flucytosine, first approved by the FDA in 1971, is an essential component in the treatment regimen for CM; however, it too is not found in most high-burden countries. Since 2017, 5 new generic sources have been approved by the FDA or the WHO Prequalification of Medicines Programme (PQP); however, this has not translated into increased access in LMICs. Insufficient testing for CM and lack of inclusion in national CM treatment guidelines has led to an unclear market demand which, in addition to unclarity on funding, does not incentivize companies to register and supply broadly.

Lack of registration is another barrier [10]. Liposomal amphotericin B from the originator is registered for use in few LMICs, and only 2 countries in sub-Saharan Africa [10]. Access to flucytosine is also limited because, among other reasons, it not registered in the majority of countries in Africa. Despite being big players in the HIV market, 2 of the generic manufacturers of flucytosine have registered only in the US but do not supply it more broadly in countries where it is needed for CM.

Twenty years ago, Médecins Sans Frontières highlighted inequities in access to another drug to prevent and treat CM, fluconazole, due to its high price, lack of competition, and irrational pricing [15]. WHO's new guidelines for CM will only translate into lives saved if a proactive approach is taken by the manufacturers and other stakeholders, together with national governments and the international community, to solving these challenges.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. 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.

2. Rajasingham R, Govender NP, Jordan A, et al. An estimate of the global burden of HIV associated cryptococcal infection in adults in 2020 [abstract EPB045]. In: International AIDS Society Conference, Montreal, Canada, July 2022.
3. World Health Organization. Guidelines for diagnosing, preventing and managing cryptococcal disease in adults, adolescents and children living with HIV. Geneva, Switzerland: WHO, **2022**.
4. Lawrence DMD, Kagimu E, Kasibante J, et al. Single high-dose liposomal amphotericin based regimen for treatment of HIV-associated cryptococcal meningitis: results of the phase-3 Ambition-cm Randomised Trial [abstract 2370]. International AIDS Society Conference, Montreal, Canada, **2020**. Available at: theprogramme.ias2021org/Abstract/Abstract/2370. Accessed 29 August 2022.
5. Lawrence DS, Tsholo K, Ssali A, et al. The Lived Experience of Participants in an African Randomised trial (LEOPARD): protocol for an in-depth qualitative study within a multisite randomised controlled trial for HIV-associated cryptococcal meningitis. BMJ Open **2021**; 11:e039191.
6. World Health Organization. Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV. Geneva, Switzerland: WHO, **2020**.
7. World Health Organization. WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. Geneva, Switzerland: WHO, **2022**.
8. Cavassin FB, Bau-Carneiro JL, Vilas-Boas RR, Queiroz-Telles F. Sixty years of amphotericin B: an overview of the main antifungal agent used to treat invasive fungal infections. Infect Dis Ther **2021**; 10:115–47.
9. Gaspani S, Milani B. Access to liposomal generic formulations: beyond AmBisome and Doxil/Caelyx. GaBI J **2013**; 2:60–2.
10. Médecins Sans Frontières. Liposomal amphotericin B: solving the access puzzle. **2021**. Available at: https://msfaccess.org/liposomal-amphotericin-b-solving-access-puzzle. Accessed 29 August 2022.
11. Banco de Preços em Saúde. Ministério da Saúde, Brasilia, Brazil. Available at: http://bps.saude.gov.br/login.jsf. Accessed 29 August 2022.
12. United Nations Development Programme. Human development report. New York: United Nations, **2020**.
13. Unitaid. Unitaid to incentivize generic production of live-saving medicine for people living with advanced HIV disease. **2022**. Available at: https://unitaid.org/news-blog/unitaid-to-incentivize-generic-production-of-life-saving-medicine-for-people-living-with-advanced-hiv-disease/#en. Accessed 29 August 2022.
14. Business Standard. Sun Pharma gets US FDA approval for amphotericin B injection. **2021**. Available at: https://www.business-standard.com/article/news-cm/sun-pharma-gets-us-fda-approval-for-amphotericin-b-injection-121121600252_1.html. Accessed 29 August 2022.
15. Perez-Casas C, Chirac P, Berman D, Ford N. Access to fluconazole in less-developed countries. Lancet **2000**; 356:2102.