ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

LIPOSOMAL AMPHOTERICIN B: Solving the access puzzle

EXECUTIVE SUMMARY

Liposomal amphotericin B (L-AmB) is an important medicine that Médecins Sans Frontières (MSF) and health ministries rely on to treat several diseases that primarily affect people who are immunocompromised, including cryptococcal meningitis and visceral leishmaniasis (also known as kala azar). L-AmB is also an essential treatment for mucormycosis (also known as black fungus), a disease that spiked in incidence in 2021 in countries like India and Nepal because of the COVID-19 pandemic.

L-AmB is unaffordable and unavailable in public healthcare systems in most low- and middle-income countries (LMICs) and not registered in all countries where people affected by these diseases live. People in these countries are left with either the conventional formulation of amphotericin B, which requires closer monitoring for side effects, or in some cases no treatment at all.

Gilead, the sole supplier of quality-assured L-AmB, has failed to deliver this lifesaving medicine at the access price of $16.25 per vial to treat cryptococcal meningitis (bringing total treatment costs to approximately $195 per person under new treatment protocols) as promised to 116 countries more than three years ago.[a,1] The company has similarly failed to provide sufficient, affordable supplies of L-AmB for visceral leishmaniasis and mucormycosis. Generic manufacturing exists but is limited due to the costs and complexities of L-AmB manufacturing, as well as challenging regulatory processes to meet safety and quality standards. These challenges, in addition to the lack of reliable demand forecasting, reduce the appeal of producing and supplying L-AmB for other prospective manufacturers. For both Gilead and generic manufacturers, lipid active pharmaceutical ingredient (API) supply shortages further constrain their efforts.

From the demand side, countries' demands for L-AmB are not reflective of true needs. A key contributing factor of this is countries' limited testing and screening for cryptococcal meningitis and visceral leishmaniasis. As a result, there is less certainty for demand forecasts. More concerningly, fewer people are diagnosed and referred to treatment. For people who are diagnosed with cryptococcal meningitis, many countries' treatment guidelines recommend conventional amphotericin B, despite increased risk of side effects. Funding programmes have similarly failed to prioritise advanced HIV disease screening,[b] testing and treatment, including for cryptococcal meningitis. Treatment funders and other global health organisations working on HIV are also limiting the effectiveness of their response by not capitalising on the insights, knowledge and mobilising potential of civil society organisations (CSOs). CSOs require funding support to bolster their knowledge and awareness about cryptococcal meningitis disease burdens and access issues and require greater inclusion in policymaking and supply discussions.

L-AmB access barriers persist due to these supply and demand challenges, and manufacturers, countries, global health funders and CSOs all have a role to play to overcome these barriers and increase access to L-AmB (Infographic 1).

© Albert Masias/MSF

A woman receives treatment at an MSF unit in Donka University Hospital in Conakry, Guinea, for cryptococcal meningitis in 2018.

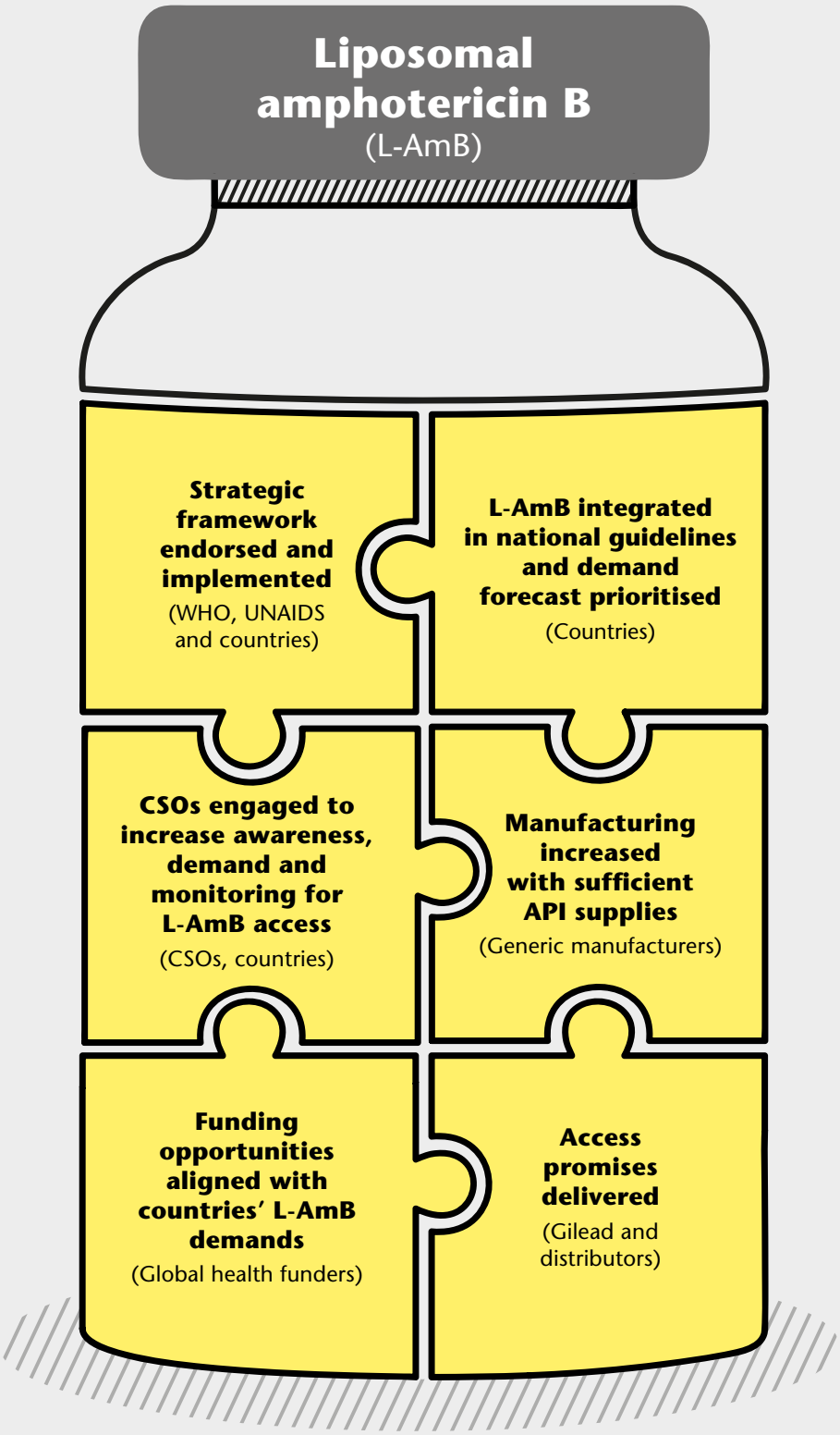
a Under the AMBITION trial treatment protocol, each person requires a single, high dose of L-AmB, which is approximately 12 vials.
b Screening for CD4 cell count <200 cells/mm3 or WHO HIV stage 3 or 4 in adults and adolescents.

MSF Access Campaign
Médecins Sans Frontières, Rue de Lausanne 78
Case postale 1016, 1211 Geneva 1, Switzerland
Tel: + 41 (0) 22 849 84 05 Fax: + 41 (0) 22 849 84 04
Email: access@msf.org **www.msfaccess.org**

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

INFOGRAPHIC 1: SOLVING THE L-AMB ACCESS PUZZLE

WHAT NEEDS TO HAPPEN AND WHO NEEDS TO DO IT



L-AMB IS A LIFESAVING TREATMENT FOR MULTIPLE DISEASES

Access to quality-assured liposomal amphotericin B (L-AmB) is critical for saving thousands of lives annually (Table 1). L-AmB is an antimycotic with antifungal and antiparasitic properties used to treat multiple diseases such as visceral leishmaniasis as well as cryptococcal meningitis, mucormycosis and other invasive fungal diseases. The first quality-assured version, marketed as AmBisome by Gilead, was developed in the 1980s and commercialised by a company called Vestar, which eventually became a division of Gilead Sciences (Gilead).[2] As of November 2021, Gilead remains the only manufacturer of quality-assured L-AmB globally.

Amphotericin B comes in several formulations. In addition to L-AmB, there is conventional amphotericin B and other lipid formulations. L-AmB is preferable to conventional amphotericin B because it is as effective and less toxic to an individual's kidneys.[3] This is especially important in settings with limited capacity to monitor kidney function. L-AmB is also preferable to other lipid formulations of amphotericin B, like amphotericin B lipid complex, for its lower toxicity and better brain penetration when treating brain infections such as cryptococcal meningitis and other difficult-to-treat fungal infections, which require high doses.

Between 2018 and 2020, MSF supplied 137,800 vials of L-AmB to 33 countries in Africa, Asia and Latin America.

Vials of liposomal amphotericin B

TABLE 1: ESTIMATED GLOBAL NEEDS FOR L-AMB ANNUALLY[c]

Disease	Estimated global disease burden	Estimated number of vials of L-AmB needed
Cryptococcal meningitis	108,000 people[4]	1,296,000 vials, annually, using the AMBITION trial protocol (approx. 12 vials/person)
Visceral leishmaniasis[5]	50,000 people[6]	450,000 vials[d]
Mucormycosis	47,572 people[e]	7,135,800 vials (approx. 150 vials/person)
Total estimated global needs	**205,572 people**	**8,881,800 vials**

c Table 1 estimates the true burden of disease (global needs). Global demands for L-AmB in terms of funding and procurement may be lower than true global needs due to demand access barriers such as lack of diagnosis, lack of country prioritisation, and misalignment of funding.

d Global distribution of cases: East Africa 50%, South Asia 25%, Americas 20% and Europe and Central Asia 5%. Estimated average weight 40 kg, as many patients are children. Treatment regimen by area in cumulative dose: East Africa 30 mg/kg, South Asia 10 mg/kg, Americas 20 mg/kg, Europe and Central Asia 20 mg/kg. Calculations based on L-AmB vial of 50 mg. Source: https://apps.who.int/iris/bitstream/handle/10665/344794/WER9635-eng-fre.pdf

e The mucormycosis outbreak was unprecedented in 2021, and it is difficult to estimate what future needs will be for L-AmB to treat the diseases. These figures are based on 2021 cases as of 3 August. Source: https://governmentstats.com/mucormycosis/index.html

L-AMB AS A TREATMENT FOR CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis is a fungal opportunistic infection of the brain and surrounding membranes affecting people who are immunocompromised, including those with advanced HIV disease (CD4 cell count <200 cells/mm3). It is one of the main causes of death of people living with HIV, accounting for 14% of all HIV-related deaths in 2020. It is second only to tuberculosis as a cause of death for people living with HIV.[4]

In July 2021, results from the AMBITION trial demonstrated that a single, high dose of L-AmB (10 vials per person) combined with two weeks of flucytosine and fluconazole was not inferior to the WHO-recommended standard seven-day regimen and was less toxic.[7] Moving from the WHO-recommended standard seven-day intravenous therapy L-AmB regimen to a regimen requiring only one day of L-AmB intravenous therapy would dramatically simplify delivery of cryptococcal meningitis treatment and save costs for people and the health system.[8] Importantly, it would ensure that people receive their full dose of L-AmB because they could receive it in one day, increasing the chance of survival. These trial results will be considered by WHO for possible inclusion in future international guidance for cryptococcal meningitis treatment.

In May 2021, a coalition including MSF put forward the "Ending Cryptococcal Meningitis Deaths By 2030" strategic framework,[9] outlining why a global strategy is needed to reduce cryptococcal meningitis deaths with key recommendations for WHO, UNAIDS, donors and countries, including making sure that earlier diagnosis and WHO-recommended cryptococcal meningitis treatments like L-AmB are available.

MSF has been treating cryptococcal meningitis for over two decades and introduced L-AmB as a cryptococcal meningitis treatment for 229 people in 2020 in Democratic Republic of Congo, Eswatini, Guinea, India and Mozambique (Box 1).

BOX 1: Access challenges for L-AmB in MSF's advanced HIV unit in Patna, India

In 2019, MSF set up a facility to treat people living with advanced HIV disease in one of the public hospitals in Patna, the capital of Bihar state in northern India. This facility is the only provider of comprehensive care for people living with HIV who have advanced HIV disease and life-threatening opportunistic infections in the country.

In November 2021, the unit was at full capacity with 40 patients hospitalised receiving treatment. Around four to five new patients, often in critical condition, visit the unit daily. Almost all have one of the numerous opportunistic infections that characterise this advanced stage of the disease, including cryptococcal meningitis, because of their immunosuppression due to a late diagnosis and initiation of antiretroviral treatment. Symptoms of cryptococcal meningitis include headaches, photophobia, blurred vision, loss of consciousness.

Dr Saumya has been working at the facility since it opened. She says when people arrive, they are seriously ill because of the advanced state of the disease caused by very delayed access to HIV treatment. Many face exclusion and stigmatisation from the public system when diagnosed with HIV. The situation can be critical for people with cryptococcal meningitis. "When the patient comes here, most of the time it is quite delayed. When they arrive they may be unconscious or have convulsions, are restless, have extremely painful headaches or visual disturbances."

Once diagnosed with cryptococcal meningitis, people are treated with L-AmB and flucytosine, which is very effective, and most people are cured as a result. Currently, L-AmB is only available for people with advanced HIV/AIDS at MSF's facility. However, it is not available to people living with HIV in any state or district hospital in Bihar. MSF has also suffered from shortages and stockouts of this medicine, as explained by Dr Shreyas, who also started at the project when it first opened. "There was a time during a COVID-19 outbreak when we experienced a scarcity of liposomal amphotericin B because the available supply had been used to treat patients with …with mucormycosis, or black fungus… we had to make difficult decisions to change the patients from liposomal amphotericin B to conventional amphotericin B… and this brought with it its own set of side effects."

Care has also been affected by prolonged and unnecessary negotiations with Gilead annually. Leena Menghaney, Head of MSF's Access Campaign in the region, explains, "Every year, we are forced to negotiate over again with the US corporation to get the medicine at the access price they have already agreed! This simply shouldn't happen. If an access price has already been set, we shouldn't have to haggle with them every single year to get the medicine at this price for our project. The delays caused by this process each year cause shortages and difficult decisions for our medical staff.

"Gilead Sciences makes a large amount of profit from this drug in the private sector, they should provide it for public HIV programmes efficiently with no quibbling over the access price…People living with HIV should not be dying in this day and age when opportunistic infections can be treated effectively and many in other countries are benefiting from the treatment."

For Dr Shreyas, access to L-AmB at the agreed access price of US$16.25 would be a game-changer for the treatment of people with cryptococcal meningitis across the state, outside MSF's facility. "Honestly, I think if we could get this medicine at this price, it is going to benefit the large population we are trying to cater for because the cost is one of the biggest aspects of why this particular drug is not being made available in the MoH hospital."

A woman receives treatment at MSF's advanced HIV disease unit in Patna, India

L-AMB AS A TREATMENT FOR VISCERAL LEISHMANIASIS

Visceral leishmaniasis, also known as 'kala azar', is a neglected tropical disease that is endemic in 78 countries. It is transmitted by the bite of a sandfly and most often affects people who live in remote and rural areas with limited access to health care. The disease is typically fatal if left untreated.

L-AmB is recommended by WHO as a treatment for visceral leishmaniasis and is included in many national treatment guidelines.[10] However, these treatment guidelines vary regionally. In India, Nepal and Bangladesh, a single high dose of L-AmB (10 mg/kg) is used to cure people, whereas people in other locations may require prolonged treatment with L-AmB over several days amounting to a higher cumulative dose (20-40 mg/kg).[11]

Cases of visceral leishmaniasis have declined in recent years. In India, Nepal and Bangladesh, the number of reported cases dropped from more than 77,000 in 1992 to under 3,200 in 2019.[12,13] In East Africa, where existing visceral leishmaniasis diagnostics and treatments are not as effective as in South Asia, more fragile progress has been made with around 11,000 cases reported in 2019.[14] The true burden is likely to be far higher due to under-reporting; WHO estimates that there are 50,000 to 90,000 new cases of visceral leishmaniasis worldwide annually.[6] In several countries where visceral leishmaniasis is endemic, seasonal outbreaks also occur, creating an additional challenge to estimating the burden of disease. Visceral leishmaniasis is still a neglected disease lacking both funding and attention. To combat this, WHO developed a Neglected Tropical Diseases 2021-2030 road map to accelerate progress towards the prevention, control and elimination of visceral leishmaniasis and other neglected diseases.[15] Now funding for implementation must follow suit.

Between 1989-2020, MSF treated almost 150,000 people with visceral leishmaniasis.[16]

L-AMB AS A TREATMENT FOR MUCORMYCOSIS

Mucormycosis (also known as 'black fungus' in India) is a rare and severe fungal infection. The fungus lives throughout the environment, is acquired by the inhalation of spores and is opportunistic, mostly affecting those with immunodeficiency, diabetes, or damaged tissue due to burns or trauma. In India, most people with COVID-19 affected by mucormycosis already had diabetes or were diagnosed while undergoing treatment for COVID-19.[17]

The disease rapidly progresses in days leading to damage of affected tissues which needs urgent surgical removal. At least half of people with mucormycosis ultimately die, and a considerable proportion of survivors suffer from long-term complications and disfiguration, including losing their eyesight.

In addition to early surgery, immediate initiation of antifungal therapy is essential. Intravenous L-AmB treatment starts with a high dose (5-10 mg/kg daily) and usually continues for weeks until there is clear improvement and the patient is stable.[18] Each person with mucormycosis may need a minimum of 150-300 vials of L-AmB. Treatment continues with other medicines for months until all disease is resolved.

The global incidence of mucormycosis is difficult to estimate as it is not a routinely reported disease. However, beginning in March 2021, in the wake of the second COVID-19 wave in India, the country experienced a sharp increase in COVID-19-associated mucormycosis cases. As of August 2021, more than 47,000 mucormycosis cases had been reported in India, and it is likely that the true numbers are higher than this.[19]

ACCESS TO L-AMB IS LIMITED BY SUPPLY AND DEMAND CHALLENGES

SUPPLY CHALLENGES: L-AMB IS NOT AFFORDABLE AND NOT SUPPLIED IN ALL COUNTRIES WHERE IT IS NEEDED

Sufficient supply of quality-assured L-AmB globally is impeded by challenges with Gilead, generic manufacturers and lipid active pharmaceutical ingredient (API) manufacturers.

1. Gilead's broken promise to ensure access to L-AmB

In 2018, Gilead announced an 'access programme' for L-AmB priced at $16.25 per vial for cryptococcal meningitis treatment in 116 low- and middle-income countries (LMICs).[1] Under the new AMBITION trial treatment protocol, this price means a full treatment course costs approximately $195 per person. In the absence of generic competition (see: 'Limited quality-assured generic manufacturing'), Gilead's commitment of an access price is crucial for people with cryptococcal meningitis. However, the company has largely failed to deliver on this promise for people with cryptococcal meningitis struggling to access L-AmB, and the programme is not available for people who need L-AmB to treat other diseases.[20]

As of November 2021, only 51 countries are confirmed to have access to Gilead's discounted price (Table 2), either through local distributors or import waivers, which allow medicines to be imported and used in the country without securing national registration. There is no information available regarding the remaining 65 countries and the supply and pricing for those countries. Even among the initial 51 countries, access issues remain. India and South Africa, for example, are eligible for Gilead's initiative, but more than three years later, MSF still faces challenges purchasing L-AmB from Gilead's distributors.

Exclusive marketing agreements between Gilead and local distributors (Key Oncologics in South Africa, Viatris in India) allow these distributors to act as market authorisation holders, granting them the final decision for L-AmB's price in the country. In South Africa, L-AmB is priced as high as $205 per vial in the private market. In India, MSF placed its annual purchase order locally in late 2020 and was offered the price of $69 per vial from Viatris. In May 2021, the MSF advanced HIV disease treatment project in Patna, Bihar, had fewer than 30 doses of L-AmB in stock and took the difficult decision to start rationing the treatment, providing it only to people with kidney failure (Box 1). After considerable pressure from civil society, Gilead and Viatris supplied 2,400 vials in June 2021 at close to the access price.[1]

TABLE 2: AVAILABILITY OF GILEAD'S ACCESS PRICE[f]

Countries where L-AmB is available at Gilead's access price through distributors, NGOs or import waivers		Countries that still do not have access to L-AmB despite being included in Gilead's list of 116 eligible countries	
1. Angola	26. Kenya	52. Afghanistan	85. Moldova
2. Benin	27. Lesotho	53. Anguilla	86. Mongolia
3. Botswana	28. Liberia	54. Antigua and Barbuda	87. Montserrat
4. Burkina Faso	29. Madagascar	55. Armenia	88. Myanmar
5. Burundi	30. Malawi	56. Aruba	89. Nauru
6. Cameroon	31. Mali	57. Bahamas	90. Nicaragua
7. Cape Verde	32. Mauritania	58. Bangladesh	91. Pakistan
8. Central African Republic	33. Mauritius	59. Barbados	92. Palau
9. Chad	34. Mozambique	60. Belarus	93. Papua New Guinea
10. Comoros	35. Namibia	61. Belize	94. Philippines
11. Congo, Democratic Republic	36. Nepal	62. Bhutan	95. Saint Kitts and Nevis
12. Congo, Republic	37. Niger	**63. Bolivia**	96. Saint Lucia
13. Cote D'Ivoire	38. Nigeria	64. British Virgin Islands	97. Saint Vincent and the Grenadines
14. Djibouti	39. Rwanda	65. Cambodia	98. Samoa
15. Equatorial Guinea	40. Senegal	66. Cuba	99. Sao Tomé and Principe
16. Eritrea	41. Seychelles	67. Dominica	100. Solomon Islands
17. Eswatini	42. Sierra Leone	68. Dominican Republic	101. Sri Lanka
18. Ethiopia	43. Somalia	69. Ecuador	102. Sudan
19. Gabon	**44. South Africa**	70. El Salvador	103. Suriname
20. Gambia	45. South Sudan	71. Fiji Islands	104. Syria
21. Ghana	46. Tanzania	72. Georgia	105. Tajikistan
22. Guinea	47. Timor-Leste	73. Grenada	**106. Thailand**
23. Guinea Bissau	48. Togo	74. Guatemala	107. Tonga
24. Honduras	49. Uganda	75. Guyana	108. Trinidad & Tobago
25. India	50. Zambia	76. Haiti	109. Turkmenistan
	51. Zimbabwe	77. Indonesia	110. Turks and Caicos
		78. Jamaica	111. Tuvalu
		79. Kazakhstan	112. Ukraine
		80. Kiribati	113. Uzbekistan
		81. Kyrgyzstan	114. Vanuatu
		82. Laos.	115. Vietnam
		83. Malaysia	116. Yemen
		84. Maldives	

f Information via Unitaid. However, countries on this list may still struggle to procure L-AmB at the promised price (e.g., India and South Africa).
(Gilead has registered L-AmB in the countries that are highlighted in **BOLD**)

In 2011, Gilead launched a donation programme for visceral leishmaniasis to support WHO in its effort to combat the disease worldwide. The donation of L-AmB is managed by WHO and is available for a limited volume and restricted set of countries to treat visceral leishmaniasis only.[g] Gilead also offers the product at discounted prices to any organisation involved in visceral leishmaniasis programmes.

The supply of L-AmB for visceral leishmaniasis programmes by Gilead has consistently been a challenge due to limited production and lack of visibility on lead time. The donation programme has also undermined incentives for registration of L-AmB in LMICs, as L-AmB is mostly supplied with an import waiver. This helps solve immediate importation issues, but the process leaves countries with unreliable and inefficient supply and should not be relied on long term.

In 2021, the sharp increase in the number of people with mucormycosis led to a temporary surge in demand for L-AmB. To respond to this urgent need, 13,420 vials of L-AmB donated to India for visceral leishmaniasis were diverted to use for mucormycosis instead.[21] Gilead was able to supply between one to two million vials of L-AmB over a period of one month through their Indian distributor, Viatris, but this was vastly insufficient as an estimated seven million vials were needed in the aftermath of the Delta wave (Table 1).[22] In June 2021, MSF and civil society organisations (CSOs) asked Gilead, Viatris, WHO and the Access to COVID-19 Tools-Accelerator (ACT-A) to take immediate action to ensure access to L-AmB for people with mucormycosis.[1,23] WHO similarly called on Gilead to reduce the price and increase supply of L-AmB for mucormycosis.[24] To date no action has been taken to meet the increased demand for L-AmB.

Across disease needs, Gilead's lack of transparency has been another challenge. Information on their annual supply capacity and volume commitments in LMICs, the list of countries where L-AmB is registered and/or supplied through import waivers, and the list of the 116 LMICs eligible for the cryptococcal meningitis access programme could help countries, CSOs and other stakeholders working to address health needs, but this is not included in their reports or publicly available.[25]

2. Limited quality-assured generic manufacturing

Having only one quality-assured manufacturer in the market is a significant risk to supply security, as starkly illustrated earlier this year when Gilead could not fulfil the urgent demands of the mucormycosis emergency. Generic manufacturing is crucial to establish a more stable supply of L-AmB and provides an opportunity to extend affordable pricing for L-AmB regardless of the disease it is used to treat.

Generic companies have been working for years to develop L-AmB and have largely overcome initial technology transfer barriers created by Gilead's refusal to share its technology. However, generic manufacturers still face multiple hurdles created by uncertainties in both global demand and regulatory requirements.

Across all three key disease indications, countries' demands for L-AmB are far lower than true global needs (see: Access barriers to diagnostic testing and screening). Creating enough global demand would help facilitate a competitive entrance of generic manufacturers to the market.

Special regulatory pathways are required for the approval of liposomal formulations of amphotericin B. They are complex to make and require complicated studies to demonstrate bioequivalence and pharmaceutical equivalence to originator products.[26] This, together with L-AmB's higher production costs relative to less complex medicines, and the limited availability of raw materials (see: Supply shortages of lipid active pharmaceutical ingredients) has significantly delayed generic competition.

Some challenges of regulatory uncertainty have begun to be addressed through multiple guidance documents, including on bioequivalence studies. However, further support is needed for generic manufacturers on other technical and regulatory issues.

While some countries with stringent regulatory authorities have issued their own guidelines on evaluating liposomal products, there is still a regulatory gap in several countries, especially countries in sub-Saharan Africa where L-AmB is most needed. Additional regulatory guidelines to develop and evaluate L-AmB and liposomal products will help generic manufacturers address critical issues of product development, manufacturing, evaluation, quality assurance and commercialisation.

Addressing L-AmB regulatory gaps is one of the keys to establishing access to generic L-AmB. In India, the Drug Controller General of India (DCGI) guidance advises manufacturers to consult US Food and Drug Administration (FDA) guidelines for evaluation of liposomal products (2019).[27] Generic manufacturers in other countries could similarly refer to this and other established regulatory guidance on liposomal product development (Box 2).

Already, some generic manufacturers are starting to produce limited quantities of L-AmB. In May 2021, with the peak increase in the number of mucormycosis cases in India, the DCGI approved five pharmaceutical companies to start manufacturing L-AmB: Alembic Pharmaceuticals, Emcure Pharmaceuticals, Gufic Biosciences, Lyca Pharmaceuticals, and Natco Pharma. This had a positive impact on extending the supply of L-AmB in India. Generic versions also exist in China.[28,29] The Chinese and Indian generic L-AmB products have not yet been WHO-prequalified or approved by a stringent regulatory authority. This may take at least two years given L-AmB's complexities.

BOX 2: List of selected guidance on the development, evaluation and commercialisation of liposomal products:

In the last decade, guidance documents on various regulatory aspects of L-AmB and liposomal products have been developed – yet ongoing support to generic manufacturers on these issues remains key.

Examples of regulatory reference documents on L-AmB published in recent years:

- February 2013: Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product **[European Medicines Agency]**[30]
- March 2016: Guideline for the Development of Liposome Drug Products **[Ministry of Health, Labour and Welfare, Japan]**[31]
- April 2018: Guidance for Industry, Liposome Drug Products **[Food and Drug Administration, US]**[32]
- August 2020: Draft Guidance on Amphotericin B (Liposomal) **[Food and Drug Administration, US]**[33]
- July 2021: Notes on the Design of Bioequivalence Study: Amphotericin B (liposomal) **[WHO]**[26]

g Donated L-AmB is available to key endemic countries such as Bangladesh, Ethiopia, India, Nepal, South Sudan and Sudan, as well as countries in East Africa where L-AmB is used to treat severe, complicated cases.

3. Supply shortages of lipid active pharmaceutical ingredients[34]

There are few lipid API manufacturers globally because before COVID-19, the market for lipid APIs was relatively small. However, lipid is the main API in L-AmB and it is also used in mRNA COVID-19 vaccines. Demand for lipids increased dramatically in 2021 due to the need for mRNA vaccines production and the millions of additional vials of L-AmB needed to respond to the mucormycosis outbreak.

In May 2021, after DCGI granted five Indian manufacturers authorisation to produce L-AmB, various lipid API manufacturers reported supply shortages. One of the main lipid suppliers, located in Germany, is overbooked with supplying orders for mRNA vaccine manufacturers for 2021 and 2022; they are not planning to take any new orders until December 2022. Another lipid API manufacturer located in India is planning to increase their manufacturing capacity from 21 kg per month to 130 kg by the end of 2021.[35]

A COVID-19 medical centre in Mysuru, Karnataka, India, where testing for COVID-19 and mucormycosis took place in June 2021

DEMAND CHALLENGES: COUNTRY DEMANDS FOR L-AMB DO NOT YET REFLECT GLOBAL NEEDS

The estimated global needs for L-AmB treatments should be reflected in country demands, but in reality the volumes countries are seeking and donors are funding is far lower than true global needs, due in part to the following issues:

1. Insufficient diagnostic testing and screening

Effectively detecting diseases requiring L-AmB treatments is a crucial step in patient care and can help countries and manufacturers understand the prevalence and possible demands for this lifesaving treatment. Unfortunately, cryptococcal meningitis and visceral leishmaniasis tests are not as accessible as they should be, while mucormycosis rapid tests do not exist, delaying treatment initiation and worsening outcomes.

Barriers to cryptococcal meningitis testing (CrAg tests) for people living with advanced HIV disease include a lack of national policies, guidelines and roll-out of CrAg tests for cryptococcal meningitis management. Where policies are in place, hospitals linked to HIV treatment centres should have uninterrupted supply of CrAg tests. They should also have training for staff at all health care levels to screen with CrAg tests and offer treatment as needed for people who test positive. Manufacturers of CrAg tests should ensure that the tests are affordable and registered in all countries that need them.

There is a large discrepancy in the estimated burden of disease of visceral leishmaniasis and the recorded number of people diagnosed; only between 25-45% of estimated cases are reported to WHO. Countries must step up their commitment and investment of resources in the control of visceral leishmaniasis. Active detection of the thousands of unidentified annual cases must be intensified to enhance disease control and ensure elimination of visceral leishmaniasis, where possible.[16]

Countries need effective tests to step up their efforts. Currently there is only one test providing a high enough sensitivity and specificity to accurately diagnose people in East Africa, US-based diagnostics company Bio-Rad's IT LEISH test. However, Bio-Rad announced they will discontinue production by mid-2022. Without IT LEISH, many additional people may go undiagnosed and will not get access to the correct treatment. To overcome this, Bio-Rad must continue the production of the rapid test until alternative manufacturers are available. Increased research and development of new, accurate point-of-care, rapid diagnostic tests for visceral leishmaniasis in East Africa is also urgently needed.

2. Lack of inclusion in national cryptococcal meningitis treatment guidelines

Due to the broader availability and the lower price of conventional amphotericin B, most national guidelines recommend it rather than L-AmB. In 2021, MSF surveyed eight countries on access and availability of L-AmB,[h] and L-AmB was not included in any of these countries' national guidelines for the treatment of cryptococcal meningitis.

Although few countries currently name L-AmB as their first-choice treatment for cryptococcal meningitis, WHO may soon recommend treatment regimens of just one day of L-AmB upon review of the AMBITION trial. This will be an opportunity for countries with a high burden of cryptococcal meningitis to take up this recommendation and prioritise L-AmB within their national treatment guidance.

Countries should consider prioritising cryptococcal meningitis treatment in their national guidelines to offer people better treatment options, further support long-term demand forecasts and avoid limited, ad-hoc funding and procurement requests. Inclusion of L-AmB in national guidelines is also a prerequisite for some donor funding eligibility, for example for procurement through the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund).

h Surveyed countries include Central African Republic, Democratic Republic of Congo, Eswatini, Guinea, India, Kenya, Mozambique and South Sudan.

3. Misalignment of donor funding for L-AmB needs

In addition to the Global Fund, the supply of L-AmB for cryptococcal meningitis is supported by global health funders such as UNITAID, the Clinton Health Access Initiative (CHAI), and the US President's Emergency Plan for AIDS Relief (PEPFAR). L-AmB and other cryptococcal meningitis treatments are also included in the Global Fund's pooled procurement mechanism, facilitated through the 'WAMBO' procurement platform, which allows countries to pool their supply orders with other countries to achieve volume-based discounts for quality-assured products.[36]

L-AmB's eligibility for this funding is an important but underutilised option. Among 79 Asian and Sub-Saharan African countries, only 13 received L-AmB from donor-funded procurement mechanisms.[i,37] It is not clear if Gilead's access price was offered to these countries. Similarly, based on MSF's survey of eight countries, only two – Democratic Republic of Congo and Mozambique – are including L-AmB in their applications for Global Fund grants in 2022.

Guidance from funders does not encourage countries' use of this funding for opportunistic infections, and this may be contributing to the limited donor-supported procurement of L-AmB. Funding envelopes do not dedicate specific portions for opportunistic infections like cryptococcal meningitis, meaning countries receiving funding must decide for themselves whether to direct funding away from more antiretroviral treatments for HIV to fund opportunistic infections. Similarly, technical teams reviewing grant applications are not challenging countries that submit applications without any funding requests for these infections.

Global health funders are also missing a key opportunity to strengthen their efforts by overlooking CSOs. CSOs, particularly networks of people living with HIV, can play a vital role in raising awareness of HIV opportunistic infections like cryptococcal meningitis and access barriers faced by people living with HIV. They can also hold countries, donors and pharmaceutical corporations to account to ensure access, affordable pricing and the adoption of the right policies and guidelines in the HIV response. Funding for CSOs' work is essential.

Elimination and control of visceral leishmaniasis is also largely donor funded. Unfortunately, the leading donor of the global leishmaniasis response, the United Kingdom, cut their overseas development assistance budget in May 2021, including funding for visceral leishmaniasis elimination programmes.[38] Several other large donors, such as the ELMA Foundation, the END Fund and the Bill and Melinda Gates Foundation had to step in to fill this immediate gap in funding on short notice, which had jeopardised disease control programmes' ability to continue their work.

Ruai Puot Malow was brought to MSF's hospital in Lankien, South Sudan, by his relatives from more than five hours away after he suffered another bout of visceral leishmaniasis in 2015. People with visceral leishmaniasis experience fever, weight loss, enlargement of the liver and spleen, anaemia and immune-system deficiencies. In South Sudan, where MSF has been treating people with visceral leishmaniasis, the risk of infection increased because of population displacement, through conflict, into areas where the disease is prevalent. With many health facilities not functioning in conflict areas, getting treatment is difficult. Testing for visceral leishmaniasis may also become more challenging since US company Bio-Rad announced they are discontinuing production of the most effective visceral leishmaniasis diagnostic test in the region.

i The 79 countries include 46 countries of sub-Saharan Africa and 33 countries in Asia where cryptococcal meningitis is present.

CONCLUSION AND RECOMMENDATIONS

Ensuring an affordable, sufficient and consistent supply of L-AmB has been an access challenge for decades with very slow progress. Gilead's broken promises, generic manufacturers' doubts about global demand and needs, lack of prioritisation of cryptococcal meningitis funding, limited funding to support CSOs' contributions, and lack of demand generation through country screening, testing and L-AmB adoption by national guidelines are current barriers.

Given L-AmB's ability to effectively treat a range of diseases, collaborative work among different stakeholders is essential to deliver Gilead's access programme promises, increase generic manufacturing, and prioritise countries' use of L-AmB. Strategic frameworks for cryptococcal meningitis and visceral leishmaniasis can also offer useful tools for countries to help them implement effective programmes and should be endorsed by WHO and UNAIDS.

KEY RECOMMENDATIONS:

1. Global action needed:

a. WHO and UNAIDS should endorse the "Ending Cryptococcal Meningitis Deaths by 2030 Strategic Framework."[9]

b. Countries should refer to this strategic framework guidance and consider integrating it into their advanced HIV disease implementation plans.

2. Gilead and distributors must deliver on Gilead's access programme promises:

a. Gilead must register L-AmB in all 116 access programme countries, offer L-AmB in these countries for the promised access price of $16.25 per vial for cryptococcal meningitis and extend this programme to other indications. Gilead must also share publicly countries of registration, the list of countries eligible for the access programme, their supply capacity, production commitments and L-AmB prices where the access programme does not yet apply.

b. Local distributors of L-AmB in South Africa (Key Oncologics) and India (Viatris, known previously as Mylan) that signed exclusive license agreements with Gilead to be the market authorisation holders in these countries must honour Gilead's access price and share their prices publicly for other indications, like mucormycosis in India.

c. Unitaid, as the host of the access price initiative for cryptococcal meningitis in collaboration with Gilead, should ensure Gilead implements the cryptococcal meningitis access programme in all 116 countries and expands this programme to other indications.

3. Increase generic manufacturing:

a. International HIV and NTD actors, in collaboration with public and private sectors, should collect and centralise L-AmB demands across different diseases and indications and share this information with generic manufacturers as an indication of global demand and needs.

b. Generic manufacturers should consider investing in L-AmB production with larger volumes and register their products in LMICs that have a burden of cryptococcal meningitis, visceral leishmaniasis or mucormycosis. They should refer to WHO or stringent regulatory authority guidance for the development of their products.

c. Lipid manufacturers should consider scaling up their production, and other API manufacturers should consider lipid production to respond to the increased global demand for lipids to produce lipid-based drug delivery systems, such as L-AmB, and mRNA vaccines.

4. Prioritise use of L-AmB in LMICs:

a. WHO should urgently consider new cryptococcal meningitis treatment guidance in light of the AMBITION trial protocol and prioritise advanced HIV disease in the new 'Global Strategy on HIV, Hepatitis B and Sexually Transmitted Infections' with specific indicators and targets.

b. Countries should consider integrating screening and testing for cryptococcal meningitis and visceral leishmaniasis. They should consider adding L-AmB, flucytosine and fluconazole to national guidelines and adopt the AMBITION regimen protocol into their national guidelines for cryptococcal meningitis, once approved by WHO. Countries should also consider including cryptococcal meningitis treatment forecasts in their grant applications to the Global Fund and other funders.

c. Diagnostic test manufacturers and suppliers should ensure affordable and sufficient supply of cryptococcal meningitis and visceral leishmaniasis tests in high-burden countries.

d. Visceral leishmaniasis programme donors should ensure predictable funding for control and elimination to achieve the WHO Neglected Tropical Diseases 2030 road map goals.

e. Global health funders such as the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR) should prioritise funding treatment of opportunistic infections such as L-AmB for cryptococcal meningitis.

f. Civil society organisations and communities should increase awareness, create demand, monitor availability of and access to L-AmB at facility levels. CSOs should integrate into their advocacy work not only HIV, but also advanced HIV disease, cryptococcal meningitis and access barriers to WHO-recommended treatments including L-AmB and flucytosine.

g. Countries, funders and WHO should continuously engage with CSOs and communities in all key decision-making processes. Global health funders should support HIV CSOs with funding to enable them to better hold stakeholders to account to remove access barriers to screening and treatment of cryptococcal meningitis.

REFERENCES

1 Open letter to Gilead and Viatris: We need affordable treatments for the rise of serious invasive fungal diseases. [Online]. 2021 Jun 23 [Cited 2021 Nov 18]. Available from: https://msfaccess.org/open-letter-ambisome-Gilead

2 Serrano D, Ballesteros M, Schatzlein A, Torrado J, Uchegbu I. Amphotericin B formulations – the possibility of generic competition. Pharmaceutical Nanotechnology. [Online]. 2013 [Cited 2021 Nov 17];1. Available from: https://www.eurekaselect.com/118030/article

3 Moore J, Proffitt R. Amphotericin B lipid preparations: what are the differences? Clin Microbiol Infect. [Online]. 2008 [Cited 2021 Nov 15]; 14(4). Available from: https://www.clinicalmicrobiologyandinfection.com/action/showPdf?pii=S1198-743X%2814%2961614-1

4 Rajasingham R. The global burden of HIV-associated cryptococcal infection: 2020 edition. [Powerpoint presentation]. Ending Cryptococcal Meningitis Deaths by 2030 – A New Global Initiative. Advanced HIV Disease Series. 2021 May 12 [Cited 2021 Nov 14]. Available from: https://iecho.unm.edu/sites/unm/download.hns?i=30835

5 MSF. Clinical guidelines: visceral leishmaniasis. [Online]. 2021 [Cited 2021 Nov 15]. Available from: https://medicalguidelines.msf.org/viewport/CG/english/leishmaniases-16689769.html#id-.LeishmaniasesvEnglish-Visceralleishmaniasis.2

6 WHO. Leishmaniasis. [Online]. 2021 May 20 [Cited 2021 Nov 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis

7 LSHTM. Ambition. [Online]. [Cited 2021 Nov 15]. Available from: https://blogs.lshtm.ac.uk/ambition/

8 WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. [Online]. 2018 [Cited 2021 Nov 24]. Available from: https://apps.who.int/iris/bitstream/handle/10665/260399/9789241550277-eng.pdf

9 Ending cryptococcal meningitis deaths by 2021- Strategic Framework. [Online]. 2021 [Cited 2021 Nov 15]. Available from: https://www.doctorswithoutborders.org/sites/default/files/documents/End%20CM%20Deaths%202030%20Strategic%20Framework.pdf

10 WHO. Frequently asked questions on visceral leishmaniasis. [Online]. 2013 [Cited 2021 Nov 24]. Available from: https://apps.who.int/iris/bitstream/handle/10665/205090/B5042.pdf?sequence=1&isAllowed=y

11 MSF. Clinical guidelines: leishmaniases. [Online]. 2021 [Cited 2021 Nov 15]. Available from: https://medicalguidelines.msf.org/viewport/CG/english/leishmaniases-16689769.html

12 Banjara M, Joshi A. Evidence for visceral leishmaniasis elimination in Nepal. Lancet Glob Health. [Online]. 2020 [Cited 2021 Nov 15]; 8. Available from: https://pubmed.ncbi.nlm.nih.gov/31981545/

13 Rijal S, Sundar S, Mondal D, et al. Eliminating visceral leishmaniasis in South Asia: the road ahead. BMJ. [Online]. 2019 [Cited 2021 Nov 17];364. Available from: https://www.bmj.com/content/364/bmj.k5224

14 WHO. WHO Global Health Observatory data repository. Number of cases of visceral leishmaniasis reported, data by country. [Online]. 2021 [Cited 2021 Nov 17]. Available from: https://apps.who.int/gho/data/node.main.NTDLEISHVNUM?lang=en

15 WHO. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030. [Online]. 2021 [Cited 2021 Nov 17]. Available from: https://www.who.int/publications/i/item/9789240010352

16 MSF. Overcoming neglect: Finding ways to manage and control NTDs. [Online]. 2021 [Cited 2021 Nov 17]. Available from: https://www.msf.org/overcoming-neglect-report-ntds

17 John T, Jacob C, Kontoyiannis D. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. J Fungi. [Online]. 2021 [Cited 2021 Nov 17];7(4). Available from: https://www.mdpi.com/2309-608X/7/4/298

18 Cornely O, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. for the Mucormycosis ECMM MSG Global Guideline Writing Group. Lancet Infect Dis. [Online]. 2019 [Cited 2021 Nov 17];19(12). Available from: https://pubmed.ncbi.nlm.nih.gov/31699664/

19 Murcormycosis. [Online]. 2021 [Cited 2021 Nov 18]. Available from: https://governmentstats.com/mucormycosis/index.html

20 Gilead. Gilead Sciences Announces Steep Discounts for Ambisome to Treat Cryptococcal Meningitis in Low- and Middle-Income Countries. Press release. [Online]. 2018 Sep 7 [Cited 2021 Nov 18]. Available from: https://www.gilead.com/news-and-press/company-statements/discount-for-ambisome

21 Government of India Ministry of Health & Family Welfare. D.O. No. 3-118/2013-NVBDCP(KA)/New Treatment.

22 Saha P. Gilead to supply 1 million Amphotericin doses as black fungus cases surge in India. India Today. [Online]. 2021 May 27 [Cited 2021 Nov 17]. Available from: https://www.indiatoday.in/india/story/gilead-to-supply-1-million-amphotericin-doses-india-black-fungus-cases-rise-1807529-2021-05-27

23 Open letter to WHO & ACT-A: We need affordable treatments for the rise of serious invasive fungal diseases that are life-threatening for COVID-19 survivors and HIV+ people. [Online]. 2021 Jun 23 [Cited 2021 Nov 18]. Available from: https://msfaccess.org/open-letter-ambisome-WHO

24 Mancini D, Asgari N, Findlay S. WHO calls for lower prices on Gilead drug for COVID-linked black fungus. Financial Times. [Online]. 2021 Jul 1 [Cited 2021 Nov 18]. Available from: https://www.ft.com/content/ced27e46-f3b1-465a-8ecc-5346d608a77f

25 Gilead. Scaling up antiretroviral treatment sustainably. [Online]. 2019 [Cited 2021 Nov 24]. Available from: https://www.gilead.com/-/media/files/pdfs/other/hiv-access-backgrounder-us-061219.pdf?la=en&hash=ECF93B60BA9576457CD62275C3D7595A

26 WHO. Notes on the design of bioequivalence study: amphotericin B (liposomal). [Online]. 2021 [Cited 2021 Nov 18]. Available from: https://extranet.who.int/pqweb/sites/default/files/documents/BE_AmphotericinB_06July2021.pdf

27 Government of India. Guidelines for Evaluation of Nanopharmaceuticals in India. [Online]. 2019 [Cited 2021 Nov 18]. Available from: https://dbtindia.gov.in/sites/default/files/uploadfiles/Guidelines_For_Evaluation_of_Nanopharmaceuticals_in_India_24.10.19.pdf

28 Zhang X, Qi H, Wang M, Ji Y, Li C, Zhao L. Pharmacokinetics of Liposomal Amphotericin B for Injection in Chinese Healthy Subjects Based on a Bioequivalence Study. Reseasrch Square. [Online]. 2021 [Cited 2021 Nov 18]. Available from: https://doi.org/10.21203/rs.3.rs-416411/v1

Continued overleaf ···

References continued

29 Choy L. Global M&A By the Numbers: Q3 2021. S&P Global. [Online]. 2021 Oct 25 [Cited 2021 Nov 18]. Available from: https://www.spglobal.com/marketintelligence/en/news-insights/blog/global-ma-infographic-q3-2021

30 EMA. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. EMA/CHMP/806058/2009/Rev. 02. [Online]. 2013 [Cited 2021 Nov 18]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-data-requirements-intravenous-liposomal-products-developed-reference-innovator_en.pdf

31 MHLW Japan. Guideline for the Development of Liposome Drug Products. [Online]. 2016 [Cited 2021 Nov 18]. Available from: https://www.nihs.go.jp/drug/section4/160328_MHLW_liposome_guideline.pdf

32 FDA. Liposome drug products. [Online]. 2018 [Cited 2021 Nov 18]. Available from: https://www.fda.gov/media/70837/download

33 FDA. Draft Guidance on Amphotericin B. [Online]. 2020 [Cited 2021 Nov 18]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_050740.pdf

34 Batra E. Black fungus: Lipids used to manufacture Liposomal Amphotericin B in shortage. CNBC TV18. [Online]. 2021 May 24 [Cited 2021 Nov 18]. Available from: https://www.cnbctv18.com/healthcare/black-fungus-lipids-used-to-manufacture-liposomal-amphotericin-b-in-shortage-9410641.htm

35 Batra E. Black fungus: Lipids used to manufacture Liposomal Amphotericin B in shortage. CNBC TV18. [Online]. 2021 May 24 [Cited 2021 Nov 18]. Available from: https://www.cnbctv18.com/healthcare/black-fungus-lipids-used-to-manufacture-liposomal-amphotericin-b-in-shortage-9410641.htm

36 The Global Fund. Procurement tools. [Online]. [Cited 2021 Nov 18]. Available from: https://www.theglobalfund.org/en/sourcing-management/procurement-tools/

37 CHAI. 2021 HIV market report. [Online]. 2021 [Cited 2021 Nov 17]. Available from: https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2021/10/2021-CHAI-HIV-Market-Report.pdf

38 Dahl E, Hamdan H, Mabrouk L, et al. Control of visceral leishmaniasis in East Africa: fragile progress, new threats. BMJ Global Health. [Online]. 2021 [Cited 2021 Nov 15];6. Available from: https://gh.bmj.com/content/6/8/e006835.info

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

MSF Access Campaign
Médecins Sans Frontières, Rue de Lausanne 78, Case postale 1016, 1211 Geneva 1, Switzerland
Tel: + 41 (0) 22 849 84 05 Fax: + 41 (0) 22 849 84 04 Email: access@msf.org

www.msfaccess.org facebook.com/MSFaccess twitter.com/MSF_access