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

23 June 2021

Dear Dr Tedros Adhanom Ghebreyesus, Dr Mariângela Simão, and co-Chairs of the ACT-A Therapeutics Pillar, Dr Phillipe Duneton and Sir Jeremy Farrar,

We are writing regarding the urgent need for liposomal amphotericin B (L-AmB) and other drugs for the treatment of severe fungal infections, including the epidemic of mucormycosis ("black fungus"), a Covid-related complication that has claimed the lives to date of more than 10,000 people and resulted in severe disfigurement of many more in India with cases now reported in Nepal. L-AmB is also a crucial treatment for cryptococcal meningitis[i], and the long-standing neglected disease, visceral leishmaniasis (kala azar),[ii] as well as other systemic fungal infections[iii].

Mucormycosis is an otherwise rare, deadly fungal infection that is increasingly affecting Covid-19 patients and survivors in India. According to the government of India, the number of mucormycosis cases increased from 9,000 in late May to 28,252 cases on 7 June 2021. Nepal is also seeing growing numbers of mucormycosis among people with Covid-19.[iv]

We are deeply concerned about the lack of sufficient, predictable, and affordable supply of L-AmB. A high volume of L-AmB vials are needed to treat mucormycosis: 150-300 vials per person.[v] In India, and perhaps now in Nepal, people are going without treatment or with suboptimal doses. Globally, an estimated 6 million vials of L-AmB are needed to treat today's cases of cryptococcal meningitis, leishmaniasis (kala azar), and mucormycosis.[vi]

Access to posaconazole (preferably delayed release tablets and injections) is also critical.[vii] While there are several manufacturers of posaconazole injection and tablets, prices remain high in the private market and governments in affected countries have yet to develop guidelines for mucormycosis and have not made the drug available.

The lack of adequate affordable supply is due to multiple factors, including:

- **High prices**: After years of pressure, Gilead finally agreed to reduce its price to US$16.25 per vial for 116 countries for the treatment of cryptococcal meningitis. However, this lower "access" price does not extend to COVID-19-related illnesses and nearly 3 years later, this lower price has been introduced in less than half (48) of the countries. Even in some of these countries, including India, treatment providers still cannot access the price of US$16.25 per vial and can face unacceptably high prices for L-AmB: a single vial can still cost as much as US$69 in India and US$200 elsewhere.[viii] This poses a significant barrier in the treatment of people living with advanced HIV disease who are critically ill with cryptococcal meningitis as well as treatment of leishmaniasis (kala azar), and mucormycosis.

- **Low supply**: Gilead has considered the liposomal technology – a key component of manufacturing L-AmB - as a trade secret,[ix] which combined with challenging regulatory pathways have undermined competition needed to contribute to a larger and more stable global supply. While there are Indian manufacturers who have begun production of L-AmB in the face of shortages, it is not clear whether the supply and timelines will meet Indian or global needs.
- **Regulatory challenges**: Gilead has the sole stringent drug regulatory authority (SDRA)/ WHO quality-assured product but as of now, has registered L-AmB in only 22 low-and middle-income countries. A non-onerous regulatory pathway is needed for pre-qualifying products from additional manufacturers.[x]

The supply and regulatory issues require leadership and urgent multifaceted action. We therefore ask that the WHO Secretariat, ACT-A Therapeutics Pillar and relevant WHO divisions, such as the Department of Essential Medicines and Health Products, HIV, NTDs, and Covid-19 teams lead on the following essential activities:

- Develop and disseminate updated guidance to governments and local stakeholders for the prevention, detection, and management of mucormycosis, including when and where L-AmB is not available.
- Develop an emergency stockpile of L-AmB and other drugs such as posaconazole to address outbreaks, including but not limited to mucormycosis.
- Generate an updated global needs assessment of L-AmB to treat cryptococcal meningitis, leishmaniasis (kala azar), mucormycosis and other indications of relevance to low and middle-income countries.
- In the short term, engage Gilead to increase manufacturing capacity of L-AmB, including supplies for India and Nepal, and offer at the lowest price (no more than $16.25 USD per vial) to governments and the private sector. Request that governments regulate these prices in the private sector.
- Carry out an assessment of supply including raw materials, manufacturers, timelines, volumes, prices, and conditions of regulatory approval of L-AmB.
- Accelerate Pre-Qualification of L-AmB generics and provide regulatory guidance for national medicines regulatory agencies (NMRAs) and further revise the WHO Pre-Qualification guidance on the design of bioequivalence studies of L-Amb, preferably so the dosing requirements are in line with the US FDA.
- Provide support to help ensure the availability of quality assured sources of oral posaconazole and isavuconazole, which are needed for treatment of mucormycosis following the intravenous treatment phase.
- Convene a L-AmB manufacturers forum to address additional needs and challenges.
- Endorse the recent strategic framework laid out by a coalition of civil society organisations, implementers, and researchers towards reducing cryptococcal meningitis deaths among people living with HIV.[xi]

We look forward to hearing from you as soon as possible, preferably by June 25, 2021 in response to the requests above. We would also like to discuss these issues further with your respective offices on July 2, 2021 at 3pm CEST/9am EST.

Sincerely, on behalf of the organizations and individuals below,

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Organisations
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Action Canada for Sexual Health and Rights, Canada
African Services Committee, Inc., United States
The AIDS and Rights Alliance for Southern Africa (ARASA), Namibia
AIDS-Free World, United States
All India Drug Action Network (AIDAN), India
APCASO, Thailand
Apvieniba HIV.LV, Latvia
Asia Pacific Network of People Living with HIV/AIDS (APN+)
Association of People Living with HIV/AIDS, Laos
Coalition of Women Living with HIV and AIDS, Malawi
Drugs for Neglected Diseases initiative (DNDi), Global
Eastern Africa National Networks of AIDS and Health Services Organization (EANNASO), Tanzania
Federation of Gender and Sexual Minorities (FSGMN), Nepal
Foundation for Integrative AIDS Research (FIAR), United States
Global Justice Now (UK), United Kingdom
Global Network of People Living with HIV (GNP+), Global
Global Network of Sex Work Projects, Scotland, United Kingdom
Health GAP, International
HIV Legal Network, Canada
Hopers Foundation, India
IFARMA Foundation, Colombia
Indonesia AIDS Coalition, Indonesia
Indonesia AIDS Coalition, Indonesia
Initiative for Medicines, Access, & Knowledge (I-MAK), United States
Khmer HIV/AIDS NGO Alliance (KHANA), Cambodia
MSF Access Campaign, Global

National Association of People living with HIV (NAPN+), Nepal
National Association of Women Living with HIV (NFWLHA), Nepal
National Network of PUD and Drug Service Organizations, Nepal
Nepalese Migrant Network, Nepal
Network Group Against AIDS-Nepal (NANGAN), Nepal
Network of Female Sex Workers (JMMS), Nepal
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People's Vaccine, Global
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Prison Foundation, Nepal
Recovering Nepal, Nepal
Sankalp Rehabilitation Trust, India
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[i] US CDC Foundation, GAFFI, St. George's University, Wits University, ITPC, University of Minnesota, DNDi, Botswana Harvard AIDS Institute Partnership, CHAI, Unitaid, University of New Mexico, LSHTM, MSF. Ending cryptococcal meningitis deaths by 2030: Strategic framework. [Online]. 2021 [Cited 2021 3 June]. Available from: https://msfaccess.org/ending-cryptococcal-meningitis-deaths-2030-strategic-framework

[ii] Sundar, S., & Chakravarty, J. (2010). Liposomal amphotericin B and leishmaniasis: dose and response. *Journal of global infectious diseases*, *2*(2), 159–166. https://doi.org/10.4103/0974-777X.62886

[iii] L-AmB is indicated for treatment of Aspergillus species, Candida species, Cryptococcus species, Histoplasmosis and talaromycosis as well as empiric therapy for presumed fungal infection in febrile, neutropenic patients

[iv] 2 dead and 11 suffering from black fungus in Nepal. *The Times of India*. 8 June 2021. [Cited 2021 12 June]. Available from: https://timesofindia.indiatimes.com/world/south-asia/2-dead-and-11-suffering-from-black-fungus-in-nepal/articleshow/83334621.cms

[v] A treatment course for mucormycosis is likely to require a minimum of 21 days before switching to oral treatment. High dosing required amounts to a high number of vials needed (e.g. 70 kg patient on AmBisome 5-10mg/kg/day would require 147(to 294 vials) for 3 weeks treatment). The calculated minimum price for a treatment course would thus be USD 10,290 (to 20,580) in the private sector.

[vi] Estimate based on: 147 vials per patient for 30,000 mucormycosis cases; 30-56 vials per patient for 14,000 visceral leishmaniasis cases, and 14 vials per patient for 108,000 cryptococcal meningitis.
[vii] In cases of L-AmB unavailability, toxicity (especially renal), invasive aspergillosis (or white fungus), and maintenance therapy following scaling down from IV liposomal amphotericin B to oral therapy, with a preference for delayed release tablets over liquid suspension.
[viii] MSF. Untangling the Web: HIV medicine pricing and access issues, 2020. [Online]. 2020 [Cited 2021 18 May]. Available from: https://msfaccess.org/untangling-web-hiv-medicine-pricing-access-issues-2020
[ix] Gilead. FORM 10-K: Annual Report Pursuant to Section 13 OR 15(d) of the Securities and Exchange Act of 1934 [Online]. 2003 [Cited 2021 12 June]. Available from: https://investors.gilead.com/node/23696/html
[x] This pathway should take into consideration that corporations such as Gilead consider essential information that could otherwise assist with regulatory approval, as protected under Article 39.3 of the TRIPS Agreement.
[xi] US CDC Foundation, GAFFI, St. George's University, Wits University, ITPC, University of Minnesota, DNDi, Botswana Harvard AIDS Institute Partnership, CHAI, Unitaid, University of New Mexico, LSHTM, MSF. Ending cryptococcal meningitis deaths by 2030: Strategic framework. [Online]. 2021 [Cited 2021 3 June]. Available from: https://msfaccess.org/ending-cryptococcal-meningitis-deaths-2030-strategic-framework