Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries

Angela Loyse, *Harry Thangaraj*, Philippa Easterbrook, Nathan Ford, Monika Roy, Tom Chiller, Nelesh Govender, Thomas S Harrison, Tihana Bicanic*

Cryptococcal meningitis is the leading cause of adult meningitis in sub-Saharan Africa, and contributes up to 20% of AIDS-related mortality in low-income and middle-income countries every year. Antifungal treatment for cryptococcal meningitis relies on three old, off-patent antifungal drugs: amphotericin B deoxycholate, flucytosine, and fluconazole. Widely accepted treatment guidelines recommend amphotericin B and flucytosine as first-line induction treatment for cryptococcal meningitis. However, flucytosine is unavailable in Africa and most of Asia, and safe amphotericin B administration requires patient hospitalisation and careful laboratory monitoring to identify and treat common side-effects. Therefore, fluconazole monotherapy is widely used in low-income and middle-income countries for induction therapy, but treatment is associated with significantly increased rates of mortality. We review the antifungal drugs used to treat cryptococcal meningitis with respect to clinical effectiveness and access issues specific to low-income and middle-income countries. Each drug poses unique access challenges: amphotericin B through cost, toxic effects, and insufficiently coordinated distribution; flucytosine through cost and scarcity of registration; and fluconazole through challenges in maintenance of local stocks—eg, sustainability of donations or insufficient generic supplies. We advocate ten steps that need to be taken to improve access to safe and effective antifungal therapy for cryptococcal meningitis.

Published **Online** June 2, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70078-1

*AL and HT contributed equally to this personal view

Cryptococcal Meningitis Group, Research Centre for Infection and Immunity, Division of Clinical Sciences, St George's University of London, UK (A Loyse MRes, Prof T S Harrison FRCP, T Bicanic BM BCh); **Access to Pharmaceuticals Project, Research Centre for Infection and Immunity, Division of Clinical Sciences, St George's University of London, UK** (H Thangaraj MBBS); **HIV Department, World Health Organisation, Geneva, Switzerland** (Prof P Easterbrook MD); **Médecins Sans Frontières and Centre for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa** (N Ford PhD); **Centre for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa** (N Ford); **Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA** (M Roy MD, T Chiller MD); **National Institute for Communicable Diseases, a Division of the National Health Laboratory Service (NHLS)** (N Govender MBBCh); **and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (N Govender)

Correspondence to: Angela Loyse, Cryptococcal Meningitis Group, Research Centre for Infection and Immunity, Division of Clinical Sciences, St George's Hospital Medical School, London SW17 ORE, UK **angelaloyse@hotmail.com**

Introduction

The right to health is firmly established in international human rights law, and encompasses the right to adequate access to health care and essential medicines.[1–4] Unfortunately, people in low-income and middle-income countries continue to face large barriers to the access of essential medicines, often with devastating consequences to individuals and public health. Essential medicines are the second largest family expenditure after food for the 90% of the population in the developing world who have to purchase medicines privately.[5] Barriers to access include drug expense, paucity of research and development on diseases predominantly affecting low-income and middle-income countries, insufficient competition from generic manufacturers, inadequate drug procurement and supply chains, and increasingly constrained global health funding.[6–12]

As a common opportunistic infection in patients with advanced HIV infection, cryptococcal meningitis is the leading cause of meningitis in adults living in sub-Saharan Africa, and contributes to up to 20% of AIDS-related deaths every year in low-income and middle-income countries.[13] Although increased access to antiretroviral therapy has resulted in a substantial reduction in incidence of cryptococcal meningitis in high-income countries,[14] the infection is likely to remain a major cause of HIV-related mortality in the foreseeable future in low-income and middle-income countries, where antiretroviral therapy coverage is insufficient and initiated at an advanced stage of HIV. In addition to delays in the diagnosis and treatment of cryptococcal meningitis, poor access to essential antifungal medicines is a major contributor to this unacceptably high mortality. Although fluconazole monotherapy is associated with increased rates of mortality, inadequate access to alternative treatments means it is widely used in the treatment of cryptococcal meningitis.[15] In this Personal View, we highlight the main obstacles to access of essential antifungal drugs for the treatment of cryptococcal meningitis in patients with HIV in low-income and middle-income countries. We review the three main antifungal drugs for cryptococcal meningitis—amphotericin B, flucytosine, and fluconazole—with respect to clinical effectiveness and access considerations specific to low-income and middle-income countries, and suggest steps to improve access to safe and effective antifungal treatment for cryptococcal meningitis.

Treatment of HIV-associated cryptococcal meningitis

Both the 2010 Infectious Diseases Society of America (IDSA) and 2011 WHO rapid advice guidelines recommend amphotericin B and flucytosine as first-line induction treatment for patients with cryptococcal meningitis, with alternative regimens tailored to individual clinical settings (table 1).[16,17] For settings in which flucytosine is unavailable, second-line induction treatment consists of amphotericin B and high-dose (800–1200 mg per day) fluconazole.[16,17] Where amphotericin B is unavailable or cannot be safely given and monitored, high-dose fluconazole and flucytosine is recommended.[16,17] The initial 2 week induction treatment is followed by consolidation and maintenance phases of treatment with fluconazole.[16–18]

Amphotericin B

Amphotericin B was introduced in the 1950s to treat systemic mycoses.[19] The drug has a broad antifungal range and only few reports of resistance have been documented.[20] Additionally, amphotericin B is used to treat visceral leishmaniasis.[21] Substantial and common side-effects of conventional amphotericin B formulations are anaemia, hypokalaemia, hypomagnesaemia, and nephrotoxicity.[22,23] These effects are reversible upon

	Amphotericin B accessible, facilities for management of toxic effects* available; flucytosine accessible	Amphotericin B accessible; flucytosine not accessible	Amphotericin B accessible, facilities for management of toxic effects* restricted; flucytosine not accessible	Amphotericin B not accessible; flucytosine accessible	Amphotericin B not accessible, facilities for management of toxic effects* not available; flucytosine not accessible
2011 WHO rapid advice guidelines[16]	Amphotericin B (0·7-1·0 mg/kg per day) and flucytosine (100 mg/kg per day)	Amphotericin B (0·7-1·0 mg/kg per day) and fluconazole (800 mg/day)	Amphotericin B (0·7-1·0 mg/kg per day) for 5–7 days, and fluconazole (800 mg/day) for 2 weeks	Fluconazole (1200 mg/day) and flucytosine (100 mg/kg per day) for ≥2 weeks	Fluconazole (1200 mg/day) for ≥2 weeks
2010 Infectious Diseases Society of America guidelines[17]	Amphotericin B (0·7–1·0 mg/kg per day) and flucytosine (100 mg/kg per day) or liposomal amphotericin B (3·0–4·0 mg/kg per day) or amphotericin B lipid complex (5·0 mg/kg per day) and flucytosine (100 mg/kg per day)	Amphotericin B (0·7–1·0 mg/kg per day) or liposomal amphotericin B (3–4 mg/kg per day) or amphotericin B lipid complex (5 mg/kg per day) or amphotericin B plus fluconazole	..	Fluconazole (800–1200 mg/day favoured) and flucytosine (100 mg/kg per day) for 6 weeks	Fluconazole (800–2000 mg/day) for 10–12 weeks or fluconazole 1200 mg/day (favoured)
2007 South African HIV Clinician Society guidelines[18]	Not applicable: flucytosine unavailable in South Africa	Intravenous amphotericin B (1·0 mg/kg per day) for 2 weeks (minimum 1 week)	Amphotericin B (1 mg/kg per day) for minimum 1 week	Not applicable: flucytosine unavailable in South Africa	Transfer patient to centre where amphotericin B available; if not possible, fluconazole (800 mg/day) for 4 weeks

All induction cryptococcal meningitis courses are for 2 weeks, unless stated. *Minimum package of prehydration, electrolyte replacement, and monitoring and management of toxic effects are available in these settings.[16]

Table 1: **Guidelines for the induction treatment of cryptococcal meningitis depending on accessibility to amphotericin B and flucytosine**

treatment termination,[23] but are concerning in settings where availability of blood transfusion and renal replacement treatment is scarce. The need for intravenous administration, monitoring of blood count and renal function, and perception of unmanageable toxic effects frequently prevent the use of amphotericin B in poorly resourced and understaffed hospital settings. Fluid and sodium loading and pre-emptive potassium replacement can reduce the risk of nephrotoxicity, and make administration of amphotericin B in low-income and middle-income countries more feasible.[24] WHO guidelines for the management of cryptococcal meningitis provide clear guidance on how to safely administer amphotericin B deoxycholate.[16]

Amphotericin B is the most rapidly acting fungicidal agent against *Cryptococcus neoformans*. On the basis of evidence from clinical trials,[23,25–31] treatment guidelines for cryptococcal meningitis recommend 2 weeks of amphotericin B-based treatment as first-line treatment, where possible.[16–18] A strategy of short-course (5–7 days) amphotericin B was associated with rapid cryptococcal clearance in two African studies,[28,31] enabling substantial reductions in both cost and toxic effects of induction treatment. Although prohibitively expensive for patients in low-income and middle-income countries, liposomal formulations of amphotericin B allow the delivery of high doses of amphotericin B and seem to be at least as effective and less nephrotoxic than conventional amphotericin B.[32,33] Bristol-Myers Squibb (USA) is the main manufacturer of amphotericin B as Fungizone. At least one US Food and Drug Administration (FDA)-approved therapeutic equivalent of amphotericin B is marketed in the USA by X-Gen Pharmaceuticals (USA).[34]

The cost of amphotericin B continues to be a barrier to access.[35] Prices range from US$3·51 to $12·20 per 50 mg vial (table 2), which is equivalent to the cost of a daily dose for cryptococcal meningitis treatment for a 50 kg adult, dosed at 1 mg/kg per day. Implementation of amphotericin B is connected with further attendant costs of hospitalisation, intravenous administration, and monitoring of toxic effects. Insufficient registration of amphotericin B is a challenge in some African countries (table 3).[37]

In 2005, Bristol-Myers Squibb was lobbied for a reduction in the price of amphotericin B in South Africa by the AIDS Law Project on behalf of the Treatment Action Campaign. The Southern African HIV Clinicians Society attained a price reduction from ZAR 146 to ZAR 26 ($18–$3) per 50 mg vial.[35] This reduction made possible the expanded use of amphotericin B and a switch away from initial fluconazole monotherapy for cryptococcal meningitis treatment in South Africa. In a survey of 25 sentinel hospitals in South Africa, the use of amphotericin B for cryptococcal meningitis induction treatment increased substantially, from 34% in 2005 to 83% in 2010.[38]

Access to amphotericin B might be further restricted by uncoordinated funding, procurement, and distribution of the drug. In low-income and middle-income countries, amphotericin B is funded, procured, and distributed by different organisations, both governmental (President's Emergency Plan for AIDS Relief, the Global Fund, UNITAID) and non-governmental (International Drug Purchase Facility, Doctors without Borders, and Clinton Health Access Initiative [CHAI]); therefore, coordination is not necessarily at country or regional levels. For example, a 2006 collaborative CHAI–UNITAID paediatric HIV/AIDS programme donated essential paediatric

	Buyer prices per 50 mg vial (US$)	Supplier	Information on supplier	Supplier prices per 50 mg vial (US$)
South Africa (Department of Health)	4·23	Mission for Essential Drugs and Supplies (MEDS), Kenya	Not-for-profit Christian organisation. Coverage: Kenya, Tanzania, Ethiopia, Sudan, and Democratic Republic of Congo. Headquarters in Nairobi.	3·51
Rwanda (Centrale d'achat des Médicaments Essentiels, Consommables et Equipements Médicaux du Rwanda)	4·65	Missionpharma (MISSION), Denmark	Supplies generic medicines, medical devices and equipment, and medical kits. Coverage: Africa, India, and China. Headquarters in Denmark.	6·35
Uganda (Uganda National Medical Store)	5·00	IDA Foundation, Netherlands	Leading not-for-profit supplier of pharmaceutical products. Supplies 3000 different medicines and medical supplies to more than 100 countries worldwide. Headquarters in Netherlands.	7·86
Namibia (Namibia Ministry of Health and Social Services)	6·97	..	..	..
Barbados Drug Service	5·27	..	..	..
Guatemalan Office of Contracting and Acquisitions	9·75	..	..	..
Costa Rica Social Security	12·20	..	..	..

Modified from Management Sciences for Health and World Health Organization,[26] by permission of Management Sciences for Health.

Table 2: **Price of amphotericin B for buyers in African and Caribbean countries**

medicines, including amphotericin B, to national HIV treatment programmes in more than 40 countries in Africa, Asia, and the Caribbean. Uptake of amphotericin B was low compared with other drugs, in part attributable to clinician unawareness of the need for, and inexperience in clinical use of amphotericin B in children (S Essajee, CHAI, personal communication).

Perceived unmanageable toxic effects as a result of insufficient local education and inadequate facilities for safe administration and monitoring are an important disincentive to clinician uptake of amphotericin B for adults with cryptococcal meningitis, even when use is recommended by guidelines. This situation causes a fall in demand, which might contribute to intermittent failures of supply chains (in both high-income and low-income countries[35]). At least three different lipid-based formulations are marketed (table 4). The most widely used liposomal intravenous formulation is AmBisome (Gilead Sciences, CA, USA), the patent of which has recently expired in several countries. Dosed at 3 mg/kg per day, it is substantially less nephrotoxic than amphotericin B, but is prohibitively expensive for low-income and middle-income countries (2011 British National Formulary list price per 50 mg vial: $150 in the UK; CIMS list price $225 in India). A substantial reduction in price to $18 per 50 mg vial was negotiated by WHO for their visceral leishmaniasis programme.[39] An equivalent price was offered by Gilead Sciences to the South African Government for treatment of patients with cryptococcal meningitis (N Geffen, Treatment Action Campaign, personal communication), but was not accepted. Gilead recently donated 445 000 vials of AmBisome for use over 5 years for the WHO visceral leishmaniasis programme.[40] Fungisome (Lifecare Innovations Ltd, India) a liposomal formulation of amphotericin B developed and trialled in India,[41] has a maximum retail price of $122 per 50 mg vial for the local market (table 4). Therefore, cost remains an important barrier to a switch from conventional to less toxic liposomal formulations of amphotericin B in low-income and middle-income countries. Cheap in-house preparations of amphotericin B lipid emulsions, with rates of nephrotoxicity comparable to liposomal formulations, warrant further efficacy studies in low-income and middle-income countries.[42]

So far, only intravenous formulations of amphotericin B have been licensed. New oral formulations of amphotericin B are in early stages of development as part of the drive to improve access to treatment for visceral leishmaniasis,[43,44] and are being developed by a Canadian firm iCoTherapeutics. Under the terms of a socially responsible licensing agreement from the University of

	Flucytosine (250 mg or 500 mg capsules)		Amphotericin B (50 mg/vial injection)		
	Registered	Availability (at supplier level)	Registered	Availability (at supplier level)	Price per vial (US$)†
Swaziland	No	No	..	Yes	4·56 and 6·25
South Africa	No	No*	Yes	Yes	3·86 and 6·11
Uganda	No	No	No	Yes	11·15
Kenya	No	No	Yes	Yes	9·71 and 4·02
Ethiopia	No	No	Yes	No	..
Sudan	No	No	Yes	Yes	3·64
Democratic Republic of Congo	No	No	Yes	No	..
Guinea	No	No	No	No	..
Cameroon	No	No	No	No	..
Tanzania	No	No	No	No	..

Data collected November–December 2011. *Through Section 21 of the Medicines Act, which allows for an unregistered medicine to be used on a named-patient basis (price=$US 1·4 per 500 mg capsule). †Prices represent supplier prices. Modified from Milani and Ford,[37] by permission of South African Medical Journal.

Table 3: **Registration, availability, and price of flucytosine and amphotericin B in ten African countries**

For **British National Formulary list prices** see http://www.bnf.org/bnf/index.htm

For **CIMS Directory Online list price data for India** see http://www.mims.com/India

	Dosage	Generic version suppliers (approved by US Food and Drug Administration)	Route of administration	Trial data available	Patent status, representative patents, or patent applications
Amphotericin B					
Bristol-Myers Squibb (USA) Fungizone	0·7-1·0 mg/kg per day	X-Gen Pharmaceuticals (USA)	Intravenous	Phase 4	Off patent
Lipid formulations of amphotericin B					
Gilead Sciences (USA) AmBisome (liposomal formulation)	3 mg/kg per day	..	Intravenous	Phase 4	Ambisome: patent expired, except possibly in the USA (patent number US5874104)
Lifecare Innovations Ltd (India) Fungisome	5 mg/kg per day	..	Intravenous	Phase 4	Fungisome: patent cooperation treaty application WO2011045809. Indian patent office application 1258/kol/09
Cephalon (UK) Abelcet (lipid complex formulation)	5 mg/kg per day	..	Intravenous	Phase 4	..
Flucytosine					
Meda Pharmaceuticals (France) Ancobon	100 mg/kg/day (four divided doses)	Sigmapharm Laboratories LLC (USA)	Oral (or nasogastrically or intravenous)	Phase 4	Off patent
Fluconazole					
Pfizer (USA) Diflucan	Variable depending on induction or maintenance phase (refer to treatment guidelines)	Glenmark Generics (USA) IVAX Sub TEVA Pharmaceuticals (USA) Mylan (USA) TEVA (Israel) Apotex (Canada) Anneal Pharmaceuticals (USA) Roxane (USA) Aurobindo Pharmaceuticals (India)	Oral (or intravenous)	Phase 4	Off patent

Data from US Food and Drug Administration.[34]

Table 4: **Formulations of antifungal drugs for cryptococcal meningitis**

British Columbia who devised the initial formulation,[45–49] iCoTherapeutics are committed to ensuring access to these formulations for treatment of visceral leishmaniasis in some low-income and middle-income countries, while allowing the company to pursue more lucrative high-income markets for treatment of fungal infections.[43,44,50]

Flucytosine

Flucytosine was created in 1957 as a potential antitumour agent, and first used to treat human candidiasis and cryptococcosis in 1968.[51,52] Flucytosine exerts its antifungal activity through rapid conversion into 5-fluorouracil,[51,53] and is available in intravenous and oral formulations, marketed as Ancotil 2·5 g/250 ml solution for infusion and Ancobon (Meda Pharmaceuticals, France) 500 mg capsules. Flucytosine is always used in combination with other antifungals because resistance emerges rapidly to monotherapy. Side-effects are mediated by 5-fluorouracil, and include gastrointestinal and bone marrow toxic effects.[53–56] Studies in low-income and middle-income countries have shown that oral flucytosine can be used safely and effectively without monitoring drug levels in settings in which complete blood count and renal function are monitored and dosing intervals are extended if renal impairment occurs.[23,26,28,30] Flucytosine can be given nasogastrically in unconscious patients.[25]

The use of flucytosine was originally restricted because of the drug's toxic effects at high doses (150 mg/kg per day); however, since the 1980s, clinical trials of cryptococcal meningitis with progressively shorter courses of flucytosine at lower doses (100 mg/kg per day) have shown that flucytosine can be used safely and effectively in combination with amphotericin B (0·7–1 mg/kg per day).[25,26,29] A trial in Vietnam showed an association between decreased mortality rates and treatment with flucytosine and amphotericin B compared with treatment with amphotericin B alone.[29] Therefore, 2 weeks of amphotericin B plus flucytosine remains the gold standard for induction treatment of cryptococcal meningitis. In low-income and middle-income countries, where amphotericin B treatment is not available or feasible, flucytosine can be safely and effectively paired with high-dose fluconazole (1200 mg/day),[57–60] as recommended by IDSA and WHO guidelines.[16,17] Despite these guideline recommendations, flucytosine is not yet available in most of Asia and Africa (table 3). The main barriers to access to flucytosine include absence of drug registration and generic drug manufacturing in low-income and middle-income countries. Flucytosine is not registered in any African country.[35,37] Flucytosine was previously marketed by Roche in South Africa, but registration of the drug lapsed in 1996.[35]

The local National Health Service trust tender price for oral flucytosine is 85p ($1·33) per 500 mg tablet for Ancobon (L Whitney, St George's Hospital Pharmacy, personal communication), or $182 for a 50 kg adult with cryptococcal meningitis receiving 14 days of induction treatment. Conversely, generic oral flucytosine, manufactured by Sigmapharm, and approved by the FDA in 2011, retails in the USA at $34 per 500 mg flucytosine tablet (A Sheppard, IMS Health, personal communication) or $4760 per 14-day course. Although flucytosine is a nucleotide analogue of simple chemical structure that has been off-patent for many years, there seems to be market failure because of insufficient demand and supply. A sustained effort is needed to make this key component of cryptococcal meningitis treatment more widely available in low-income and middle-income countries.

Fluconazole

Fluconazole has excellent bioavailability and cerebrospinal fluid (CSF) penetration and few adverse effects.[61,62] The drug is available in intravenous formulation and is commonly given orally to treat cryptococcal meningitis. Clinical and mycological outcomes in trials of low-dose fluconazole monotherapy (200–400 mg/day) as induction treatment have been disappointing, with high mortality and prolonged time to CSF sterilisation.[15,63,64] This slow fungal clearance can predispose to development of secondary drug resistance and cryptococcal immune reconstitution syndrome.[65–67] Phase 2 studies[30,68] with high-dose fluconazole in combination with amphotericin B yielded good mycological and clinical outcomes and, in a larger trial, no difference in 2 week and 10 week mortality was evident between amphotericin B plus fluconazole 800 mg/day and amphotericin B plus flucytosine.[29] Therefore, WHO and IDSA guidelines recommend the use of amphotericin B with high-dose fluconazole as second-line induction antifungal regimens.[16,17]

Higher doses of fluconazole (800–1200 mg/day) as induction treatment are well tolerated and have faster rates of fungal clearance than a dose of 400 mg daily.[69] Clearance rates are further improved when fluconazole is combined with flucytosine.[57,58] WHO guidelines include high-dose fluconazole monotherapy as an induction treatment option (table 1), but only when amphotericin B and flucytosine are unavailable.[16]

Fluconazole is also a cornerstone of consolidation and maintenance treatment of cryptococcal meningitis[16–18] with published guidelines recommending step-down to fluconazole after the initial 2 week induction to prevent recurrence of disease.[16–18] Since 2012, fluconazole has also been used to treat early cryptococcal disease detected through cryptococcal antigen screening.[70] Pre-emptive treatment of patients with a CD4 count less than or equal to 100 cells per µL and asymptomatic cryptococcal antigenaemia with fluconazole is being piloted in South Africa as a public health strategy to reduce death and morbidity caused by cryptococcal meningitis.[67,71]

Fluconazole is off patent, generally widely available and cheap, and numerous generic versions have FDA approval (table 4, price range with WHO Global Price Reporting Mechanism: $0·08–$1·36 per day when dosed at 800 mg[36]). Although cost has greatly restricted access to fluconazole in the past,[72] availability has gradually improved through increased production by generic manufacturers. Since 2000, Pfizer's (NY, USA) Diflucan Partnership programme has provided free Diflucan to 63 low-income and middle-income countries for the treatment of patients with cryptococcal meningitis and oesophageal candidiasis (not for the pre-emptive treatment of cryptococcal antigenaemia) and is set to continue indefinitely (Diflucan Partnership programme, Pfizer, personal communication). However, implementation of the programme varies: at teaching hospital pharmacies at investigators' collaborating trial sites in South Africa (Cape Town, Pietermaritzburg, and Durban) and Uganda (Mbarara and Kampala), donated Diflucan is readily available, whereas in Malawi (Blantyre and Lilongwe), Zambia (Lusaka), Cameroon (Douala and Yaoundé), and Tanzania (Arusha), purchased generic fluconazole rather than donated Diflucan is in stock, attributable to the challenges of sustaining timely and streamlined ordering through the donation programme. Although free fluconazole has been crucial for the treatment of cryptococcal meningitis in Africa, increased availability of fluconazole by comparison with amphotericin B might have led to clinicians favouring fluconazole over amphotericin B-based induction treatment.[73,74]

Recommendations for improvement of access to antifungals

We propose ten measures to improve access to cryptococcal meningitis treatment (panel). Improved estimates of disease burden, building upon studies by the CDC,[13] either via national cryptococcal surveillance systems (eg, South African National Institute for Communicable Diseases)[75] or through localised epidemiological studies, would help with drug forecasting, streamline ordering, and maximise the use of donations. Such data would allow estimates of market size for manufacturers to be made and allow competitive price negotiation.

The 2011 WHO rapid advice guidelines[16,76] provide recommendations on antifungal regimens tailored to clinical settings (table 1), and offers guidance on how to minimise toxic effects and monitor amphotericin B,[16–18] so that increased access does not produce more harm than good. These recommendations need to be translated into country-specific or region-specific treatment guidelines,[18] and implemented alongside capacity building measures to improve facilities for rapid diagnosis, monitoring of toxic effects, and fast-track referral into antiretroviral therapy programmes.

In the WHO Model List of Essential Medicines,the core (the most efficacious, safe and cost-effective medicines for priority conditions for use in a basic health-care

For **WHO Global Price Reporting Mechanism** see http://apps.who.int/hiv/amds/price/hdd/t

For the **Diflucan Partnership programme** see http://www.diflucanpartnership.com

For the **South African National Institute for Communicable Diseases** see http://www.nicd.ac.za

For the **WHO Model List of Essential Medicines** see http://www.who.int/medicines/publications/essentialmedicines/en/

Panel: **Ten measures to improve access to antifungal drugs for the treatment of cryptococcal meningitis**

- Improve estimates of cryptococcal meningitis disease burden
- Ensure wider dissemination of best clinical practice
- Include all cryptococcal meningitis drugs on WHO core Essential Medicines List
- Register antifungals in low-income and middle-income countries
- Pooled procurement of antifungals
- Increase competition through generation of generics
- Ensure preferential pricing for low-income and middle-income countries by pharmaceutical companies
- Ensure socially responsible licensing of intellectual property for new antifungals or formulations developed by research organisations
- Optimise existing antifungal strategies in clinical trials in low-income and middle-income countries
- Stimulate research and development of novel antifungals by designation of cryptococcal meningitis as a neglected disease

system) list includes only fluconazole, while amphotericin B and flucytosine, despite their greater effectiveness in treatment of cryptococcal meningitis, are on the complementary list. Amphotericin B and flucytosine should be included in the core list and national essential medicine lists and exempted from import duties and taxes.[5–11] Antifungal drugs should be registered in low-income and middle-income countries, and a requirement to show bioequivalence, quality standards (ie, good manufacturing practice), and effectiveness of new generic formulations should be included. In many low-income and middle-income countries, medicines regulatory authorities are hampered by insufficient resources and human capacity. Successful registration of antifungal drugs might need support from experienced authorities such as the Medicines Control Council of South Africa, the FDA, or European Medicines Agency,[77] or even the introduction of a pan-African reciprocal drug-approval process. In South Africa, efforts are underway for fast-track registration of flucytosine with the Medicines Control Council (C Chuma, Lighthouse Healthcare, personal communication).

Drug companies should include antifungals in corporate responsibility policies on HIV, and consider preferential pricing for low-income and middle-income countries. Increased competition through generation of generics is needed. Generic pharmaceutical manufacturers should be given incentives and manufacturing support to produce generic versions of flucytosine for the low-income and middle-income country markets. South Africa is exploring the manufacture of cheaper generic flucytosine at facilities contracted by GSK and Pfizer in Bangladesh; a lengthy process that needs a full Medicines Control Council inspection (C Chuma, Lighthouse Healthcare, personal communication). Pooled procurement of antifungals would increase availability and secure competitive prices, through effective coordination of regional governments, global health organisations and funders, and pharmaceutical companies and distributors.[78] Drug funding and distribution could be integrated with existing antiretroviral therapy programmes to provide antifungals alongside antiretrovirals, antituberculous drugs, and co-trimoxazole.

The optimisation of antifungal regimens in mortality-endpoint trials in low-income and middle-income countries is a driver for policy change. A multicentre African phase 3 trial (ISRCTN 45035509) is comparing standard with short-course amphotericin B-based regimens and a purely oral combination (ie, fluconazole plus flucytosine). Additionally, socially responsible licensing of intellectual property[79] should apply to new antifungals or formulations made through research funded by the public or by foundations. To our knowledge, only one new long-acting azole-like compound is in development in a joint project between Viamet pharmaceuticals and the NIH Therapeutics for Rare and Neglected Diseases programme.[80] The scarcity of drug development for cryptococcal meningitis is in stark contrast to the range of new drugs emerging from product-development partnerships for the treatment of malaria and tuberculosis,[81] diseases that are associated with a comparable mortality burden to cryptococcal meningitis in sub-Saharan Africa.[13]

The research and advisory group Policy Cures lists three criteria essential to classify a disease as neglected:[81] the disease must predominantly affect people in low-income countries; needs new, improved, or additional products; and suffers from market failure because of an insufficient commercial market, resulting in insufficient research and development by industry. Cryptococcal meningitis fulfils all of these criteria. Official classification of cryptococcal meningitis as a neglected disease would help attract funding for drug development.

Conclusions

Although continued global scale-up of antiretroviral therapy and initiation before the CD4 count falls below 350 cells per μL remains the most important long-term strategy to reduce the incidence of cryptococcal meningitis, the infection will remain a major cause of HIV-related morbidity and mortality, particularly in sub-Saharan Africa in the foreseeable future. Treatment for cryptococcal meningitis relies on three old, off-patent antifungal drugs, which each pose specific access challenges for low-income and middle-income countries: amphotericin B through cost, toxic effects, and insufficiently coordinated distribution; flucytosine through cost and insufficient registration; and fluconazole through challenges to maintenance of local stocks, be it through sustainability of

 Published online June 2, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70078-1

donations or insufficient generic supplies. If patients with cryptococcal meningitis survive the acute disease and become established on antiretroviral therapy, long-term prognosis is excellent.[15] It is unacceptable that up to one half of patients with cryptococcal meningitis in low-income and middle-income countries do not survive to 10 weeks, and do not benefit from expansion of antiretroviral therapy programmes, partly because even the basic range of antifungal drugs is not available to them.

Access to the most effective antifungal drugs for treatment of cryptococcal meningitis in developing countries needs to be urgently improved as part of the global response to the HIV pandemic. A concerted move away from the widely-practised fluconazole monotherapy, towards more effective combination induction treatment regimens including amphotericin B or flucytosine or both, is needed. A coordinated international effort should involve relevant public and private organisations and we must learn from models with proven success in the implementation of access to medicines for other important global infectious diseases. Facilitated by WHO, a meeting of key stakeholders took place in March 2013 and has given rise to a concerted advocacy effort to improve access to essential antifungals for cryptococcal meningitis.

Contributors

The concept and structure of the manuscript was devised by HT, AL, TB, TSH. AL, HT, MR, PE, NG, TB collated data, including drug costings. AL, HT, and TB wrote the first draft of the manuscript. All authors contributed to writing and editing the final manuscript.

Conflicts of interest

HT is funded by a European Union grant (FP7 Health 241839). TB is funded by a Wellcome Trust Intermediate Fellowship (WT 089966). The findings and conclusions of this personal view are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The use of product names in this manuscript does not imply their endorsement by the US Department of Health and Human Services.

Acknowledgments

The following people kindly provided or collated information on local or international antifungal drug prices or both: Iman Wanis and Boniface Dongmo Nguimfack (WHO, Switzerland), Alan Sheppard (IMS Health, USA), and Laura Whitney (St George's Hospital Pharmacy, London, UK). Chomba Chuma of Lighthouse Healthcare (Johannesburg, South Africa) is exploring registration and manufacture of generic flucytosine for South Africa, and provided relevant information on this process. Shaffiq Essajee (CHAI, USA) provided unpublished information regarding the uptake of amphotericin B through the CHAI UNITAID donation. We thank Richard Mahoney of the International Vaccine Institute (Seoul, South Korea) for critical reading of the manuscript, and Nathan Geffen of the Treatment Action Campaign (Cape Town, South Africa) for information regarding price negotiations for liposomal amphotericin B. We thank David Boulware (University of Minnesota, USA) and Mark Jacobson (Selian Hospital, Arusha, Tanzania) for providing information regarding Diflucan availability in Arusha, Tanzania.

References

1 World Health Organization. Constitution of the World Health Organization. New York; WHO, 1946.
2 United Nations General Assembly. Universal Declaration of Human Rights. Paris; United Nations, 1948.
3 United Nations General Assembly. International covenant on economic, social and cultural rights (ICESCR). New York; United Nations, 1976.
4 United Nations. General Comment No. 14 (2000). The right to the highest attainable standard of health (article 12 of the International Covenant on Economic, Social and Cultural Rights). http://www.unhchr.ch/tbs/doc.nsf/(Symbol)/40d009901358b0e2c1256915005090be?Opendocument (accessed April 26, 2013).
5 World Health Organization. Equitable access to essential medicines: a framework for collective action. WHO Policy Perspectives on medicines. March 2004. whqlibdoc.who.int/hq/2004/WHO_EDM_2004.4.pdf (accessed April 26, 2013).
6 Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access to medicines for all. *J Int AIDS Soc* 2011; **14:** 15.
7 Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. *Global Health* 2011; **7:** 39.
8 World Health Organization. Access to medicines. Intellectual property protection: impact on public health. *WHO Drug Information* 2005; **19:** 236–41.
9 Smith RD, Correa C, Oh C. Trade, TRIPS, and pharmaceuticals. *Lancet* 2009; **373:** 684–91.
10 Cameron C, Ewen M, Ross-Degnen D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet* 2009; **373:** 240–49.
11 Médecins Sans Frontières. Campaign for Access to Essential Medicines. Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries. 13th Edition July 2010. Geneva: Médecins Sans Frontières, 2006.
12 The Global Fund. Options for modification of the application, renewal and approval processes for new and existing investments. 25th board meeting; Accra, Ghana, Nov 21–22, 2011. http://www.theglobalfund.org/en/board/meetings/twentyfifth/documents/ (accessed April 26, 2013).
13 Park BJ, Wannemuehler KA, Marston BJ, et al. Estimation of the global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 2009, **23:** 525–30.
14 Mirza SA, Phelan M, Rimland D. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. *Clin Infect Dis* 2003; **36:** 789–94.
15 Bicanic T, Jarvis J, Loyse A, et al. Determinants of acute outcome and long-term survival in HIV-associated cryptococcal meningitis: results of a combined cohort of 523 patients. 18th conference on retroviruses and opportunistic infections; Boston, USA; Feb 27–Mar 2, 2011. 892.
16 World Health Organization. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and childrenGeneva: WHO, Dec 2011. http://www.who.int/hiv/pub/cryptococcal_disease2011/en/index.html. (accessed Aug 6, 2012).
17 Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; **50:** 291–322.
18 South African HIV Clinicians Society. Guidelines for the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV- infected patients. Cape Town; Health and Medical Publishing Group, 2007. http://www.sahivsoc.org/practise-guidelines/sa-hiv-clinicians-society-guidelines (accessed Aug 10, 2012).
19 Brajtburg J, Powderly WG, Kobayashi GS, Medoff G. Amphotericin B: current understanding of mechanisms of action. *Antimicrob Agents Chemother* 1990; **34:** 183–88.
20 Ellis D. Amphotericin B: spectrum and resistance. *J Antimicrob Chemother* 2002; **49** (suppl 1)**:** 7–10.
21 Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011; **377:** 477–86.
22 Thakur CP, Kumar A, Mitra DK, Roy A, Sinha AK, Ranjan A. Improving outcome of treatment of Kala-Azar by supplementation of amphotericin B with physiologic saline and potassium chloride. *Am J Trop Med Hyg* 2010; **83:** 1040–43.
23 Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: A randomised trial. *Clin Infect Dis* 2008; **47:** 123–30.

24 Bahr N, Rolfes MAR, Musubire B, et al. The impact of routine electrolyte supplementation during amphotericin induction therapy in resource-limited settings. 8th International Conference on Cryptococcus and Cryptococcosis; Charleston, USA; May 1–5, 2011. 183.

25 Van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immuno-deficiency syndrome. *N Engl J Med* 1997; **337:** 15–21.

26 Brouwer A, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated Cryptococcal Meningitis: a randomised trial. *Lancet* 2004; **364:** 1764–67.

27 Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis* 2007; **45:** 76–80.

28 Jackson AT, Nussbaum JC, Phulusa J, et al. A phase II randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis *AIDS* 2012; **26:** 1363–70.

29 Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for HIV-associated cryptococcal meningitis. *N Engl J Med* 2013; **368:** 1291–302.

30 Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis* 2012; **54:** 121–28.

31 Muzoora CK, Kabanda T, Ortu G, et al. Short course AmB with high-dose fluconazole for HIV-associated cryptococcal meningitis. *J Infect* 2012; **64:** 76–81.

32 Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS* 1997; **11:** 1463–71.

33 Hamill RJ, Sobel RD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomised, double-blind clinical trial of efficacy and safety. *Clin Infect Dis* 2010; **51:** 225–32.

34 US Food and Drug Administration. FDA orange book: approved drug product with therapeutic equivalence evaluations. Rockville; Orange Book Publications, 2011.

35 Bicanic T, Wood R, Bekker L-G, Darder M, Meintjes G, Harrison TS. Antiretroviral roll-out, antifungal roll-back: Access to treatment for cryptococcal meningitis. *Lancet Infect Dis* 2005; **5:** 530–31.

36 Management Sciences for Health and World Health Organization. 2012. International Drug Price Indicator Guide 2011. Frye JE, ed. http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2011_en.pdf (accessed May 21, 2013).

37 Milani B, Ford N. Responding to the evidence for improved treatment for cryptococcal meningitis in resource-limited settings. *S Afr Med J* 2012; **102:** 196–97.

38 Govender N. Cryptococcosis in developing countries: where are we after a decade of population-based surveillance in South Africa. 8th international conference on climate change; Charleston, USA; May 1–5, 2011. 22.

39 World Health Organization. Report of a WHO informal consultation on liposomal amphotericin B in the treatment of visceral leishmaniasis. Rome; World Health Organization, April 16, 2005.

40 Gilead Sciences and WHO establish new five year initiative to prevent deaths from visceral leishmaniasis. National AIDS Treatment Advocacy Project. http://www.natap.org/2011/newsUpdates/121211_04.htm (accessed April 26, 2013).

41 Jadhav MP, Bamba A, Shinde VM, et al. Liposomal amphotericin B (Fungisome™) for the treatment of cryptococcal meningitis in HIV/AIDS patients in India: a multicentric, randomized controlled trial. *J Postgrad Med* 2010; **56:** 71–75.

42 Mistro S, Maciel Ide M, de Menenzes RG, et al. Does lipid emulsion reduce amphotericin B nephrotoxicity? A systematic review and meta-analysis. *Clin Infect Dis* 2012; **54:** 1774–77.

43 Wasan KM, Thornton SJ, Bell I, et al. The global access initiative at the University of British Columbia (UBC): Availability of UBC discoveries and technologies to the developing world. *J Pharm Sci* 2009; **98:** 791–94.

44 The Alliance for Case Studies for Global Health. Case studies for global health. Building relationships. Sharing knowledge. http://www.mmv.org/newsroom/publications/case-studies-global-health. (accessed June 12, 2012).

45 Sachs-Barrable K, Lee SD, Wasan EK, Thornton SJ, Wasan KM. Enhanced drug absorption using lipids: A case study presenting the development and pharmacological evaluation of a novel lipid-based oral Amphotericin B formulation for the treatment of systemic fungal infections. *Adv Drug Deliv Rev* 2008; **60:** 692–701.

46 Thornton SJ, Wasan KM, Piecuch A, Lynd LL, Wasan EK. Barriers to treatment for visceral leishmaniasis in hyperendemic areas: India, Bangladesh, Nepal, Brazil and Sudan. *Drug Dev Ind Pharm* 2010; **36:** 1312–19.

47 Wasan EK, Gershkovich P, Zhao J, et al. A novel tropically stable oral amphotericin B formulation (iCo-010) exhibits efficacy against visceral Leishmaniasis in a murine model. *PLoS Negl Trop Dis* 2010; **4:** e913.

48 iCo Therapeutics. Oral amphotericin B delivery system. http://www.icotherapeutics.com/pipeline/ico009/ (accessed June 12, 2012).

49 Gershkovich P, Sivak O, Wasan EK, et al. Biodistribution and tissue toxicity of amphotericin B in mice following multiple dose administration of a novel oral lipid-based formulation (iCo-009). *J Antimicrob Chemother* 2010; **65:** 2610–13.

50 Busang R, Boisjoly-Letourneau K, Bernard Fourie, Mulder M, Thangaraj H. Socially responsible licensing of health technologies; policy and practice in South Africa. *LES J* 2011; **2:** 69–77.

51 Duchinsky R, Pleven E, Heidelberger C. The synthesis of 5-fluoropyrimidines. *J Am Chem Soc* 1957; **79:** 4559–60.

52 Tassel D, Madoff MA. Treatment of candida sepsis and cryptococcus meningitis with 5-fluorocytosine. A new antifungal agent. *JAMA* 1968; **206:** 803–32.

53 Bennett J. E Flucytosine. *Ann Intern Med* 1977; **86:** 319–21.

54 Block ER, Bennett JE. Pharmacological studies with 5-fluorocytosine. *Antimicrob Agents Chemother* 1972; **1:** 476–82.

55 Vermes A, Guchelaar H-J, Dankert J. Flucytosine: a review of its pharmacology,clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46:** 171–79.

56 Brouwer AE, van Kan HJ, Johnson E, et al. Oral versus intravenous flucytosine in patients with human immunodeficiency virus-associated cryptococcal meningitis. *Antimicrob Agents Chemother* 2007; **51:** 1038–42.

57 Nussbaum JC, Jackson A, Namarika D, et al. A randomised-controlled trial of addition of flucytosine to high-dose fluconazole for treatment of HIV-associated cryptococcal meningitis in Malawi 2009. *Clin Infect Dis* 2010; **50:** 338–44.

58 Larsen RA, Bozette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* 1994; **19:** 741–45.

59 Mayanja-Kizza H, Oishi K, Mitarai S, et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. *Clin Infect Dis* 1998; **26:** 1362–66.

60 Milfechik E, Leal MA, Haubrich R, et al. Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis. *Med Mycol* 2008; **46:** 393–95.

61 Palou de Fernandez E, Patino MM, Graybill JR, Tarbit MH. Treatment of cryptococcal meningitis in mice with fluconazole. *Antimicrob Agents Chemother* 1986; **18:** 261–70.

62 Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. *Antimicrob Agents Chemother* 1988; **32:** 1–8.

63 Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad Med J* 2001; **77:** 769–73.

64 Schaars CF, Meintjes GA, Morroni C, Post FA, Maartens G. Outcome of AIDS-associated cryptococcal meningitis initially treated with 200mg/day or 400mg/day of fluconazole. *BMC Infect Dis* 2006; **6:** 118.

65 Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G. Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. *Clin Infect Dis* 2006; **43:** 1069–73.

66 Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. *AIDS* 2005; **19:** 2050–52.

67 Jarvis JN, Lawn SD, Vogt M, et al. Screening for cryptococcal antigenaemia in patients accessing an antiretroviral treatment program in South Africa. *Clin Infect Dis* 2009; **48:** 856–62.

68 Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of Amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis* 2009; **48:** 1784–86.

69 Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in Southwestern Uganda. *Clin Infect Dis* 2008; **47:** 1556–61.

70 South African Department of Health. National strategic plan on HIV, STIs, and TB 2012–16. Feb 15, 2012. Cape Town. http://www.doh.gov.za/docs/stratdocs/2012/NSPfull.pdf (accessed April 29, 2013).

71 Jarvis J, Harrison TS, Govender N, et al. Routine cryptococcal antigen screening for HIV-infected patients with low CD4+ T-lymphocyte counts—time to implement in South Africa? *S Afr Med J* 2011; **101:** 232–34.

72 Perez-Casas C, Chirac P, Berman D, Ford N. Access to fluconazole in less-developed countries. *Lancet* 2000; **356:** 2102.

73 Hamill RJ. Free fluconazole for cryptococcal meningitis: too little of a good thing? *Clin Infect Dis* 2006; **43:** 1074–76.

74 Collett GG, Parrish AA. Fluconazole donation and outcomes assessment in cryptococcal meningitis. *S Afr Med J* 2007; **97:** 175–76.

75 Meiring ST, Quan VC, Cohen C, et al. A comparison of paediatric- and adult-onset cryptococcosis detected through population-based surveillance in South Africa, 2005–2007. *AIDS* 2012; **26:** 2307–14.

76 Doctors without Borders. First ever treatment guidelines released for major cause of death of people living with HIV. Addis Ababa; Dec 7, 2011. http://www.doctorswithoutborders.org/press/release.cfm?id=5654 (accessed June 12, 2012).

77 Moran M, Guzman J, McDonald A, Wu L, Omune B. Registering new drugs; the African context. New tools for new times. Jan, 2010. http://www.policycures.org/downloads/DNDi_Registering_New_Drugs-The_African_Context_20100108.pdf (accessed April 26, 2013).

78 Waning B, Kaplan W, King AC, Lawrence DA, Leufkens HG, Fox MP. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. http://www.who.int/bulletin/volumes/87/7/08-058925/en/ (accessed May 16, 2012).

79 Thangaraj H, Reljic R. Social leverage of intellectual property: road to the development of better therapy for tuberculosis. *Recent Pat Antiinfect Drug Discov* 2009; **4:** 114–22.

80 Najvar LK, Wiederhold NP, Fothergill AW, et al. The novel fungal Cyp51 inhibitor VT-1129 demonstrates potent in vitro and in vivo against Cryptococcus species. 8th International conference on cryptococcus and cryptococcosis. Charleston, USA; May 1–5, 2011.

81 Drake P, Thangaraj H. Molecular farming, patents and access to medicines. *Expert Rev Vaccines* 2010; **9:** 811–19.

82 Moran M, Guzman J, Abela-Oversteegen L, et al. Neglected disease research and development: Is innovation under threat? Policy Cures G-Finder Report. Dec, 2011. http://www.policycures.org/projects.html (accessed June 12, 2012).