

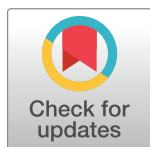
VIEWPOINTS

Cryptococcal meningitis: A neglected NTD?

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Although HIV/AIDS has been anything but neglected over the last decade, opportunistic infections (OIs) are increasingly overlooked as large-scale donors shift their focus from acute care to prevention and earlier antiretroviral treatment (ART) initiation. Of these OIs, cryptococcal meningitis, a deadly invasive fungal infection, continues to affect hundreds of thousands of HIV patients with advanced disease each year and is responsible for an estimated 15%–20% of all AIDS-related deaths [1, 2]. Yet cryptococcal meningitis ranks amongst the most poorly funded “neglected” diseases in the world, receiving 0.2% of available relevant research and development (R&D) funding, according to Policy Cures’ 2016 Global Funding of Innovation for Neglected Diseases (G-Finder) Report [3, 4].

Although cryptococcal meningitis is not formally recognised by the World Health Organisation (WHO) or *PLOS Neglected Tropical Diseases* (*PLOS NTDs*) as a neglected tropical disease (NTD), it is listed in the G-Finder report, as it disproportionately affects people in low- and middle-income countries (LMICs), with market failure evident for existing essential antifungal medicines and an urgent need for new, effective, and less toxic medicines. *PLOS NTDs* defines NTDs as a “group of poverty-promoting chronic infectious diseases, which primarily occur in rural areas and poor urban areas of LMICs” [5] and according to the WHO, NTDs are “a proxy for poverty and disadvantage”, have “an important impact on morbidity and mortality”, and are relatively “neglected by research” [6]. Although the greatest burden of cryptococcal disease is undoubtedly related to HIV, we demonstrate herein that cryptococcal meningitis meets both the WHO and *PLOS NTDs* definitions of an NTD,

as the disease (1) disproportionately affects populations in poverty and causes substantial morbidity and mortality, (2) primarily affects populations living in tropical and subtropical areas, (3) is immediately amenable to broad control, elimination, or eradication, and (4) is neglected by research [7].

Morbidity, mortality, and poverty associated with cryptococcal meningitis

As the most common cause of meningoencephalitis in sub-Saharan Africa and Southeast Asia, cryptococcal meningitis disproportionately affects populations in some of the most economically disadvantaged regions of the world [1–3]. Mortality rates remain high, ranging between 20% and 60% with treatment and up to 100% without, affecting the most economically productive age groups [1, 8–11]. Significant morbidity is often encountered, with severe headaches occurring weeks to months before presentation and potential long-term sequelae including blindness and deafness [12–14]. Such morbidity and mortality places a substantial economic burden on patients and their families, resulting in lost productivity and wages as well as patient-transportation and medical costs. Effective treatments are intensive, expensive (for example, where available, first-line induction therapy with amphotericin B therapy costing over US\$200 in Uganda), and available only in hospitals (due to the need for intravenous [IV] administration of amphotericin B and need for close laboratory monitoring for toxicities) [15, 16].

A disease of the tropics and subtropics

ART scale-up is ultimately the key to reducing cryptococcal meningitis mortality, as has been demonstrated in Europe and North America [17, 18]. However, the burden of morbidity and mortality in LMICs has remained largely unchanged and shows no sign of abating [2, 19–22]. The number of severely immunosuppressed patients not yet accessing ART has remained relatively constant and, in some instances, even increased [23–28]. Data from a recent meta-analysis estimated that over half of patients in Africa had progressed to AIDS with CD4 counts <200 cells/mm³ by the time they initiated ART [29], despite over a decade of ART program implementation and scale-up.

While new WHO guidance on a strategy of universal HIV testing and treatment has the potential to prevent cryptococcal disease, poor retention in care and ART failure currently have a significant impact on the incidence of cryptococcal meningitis in Africa. In many hospitals, over half of cryptococcal meningitis cases now occur in patients previously prescribed ART, either in the early months following initiation of ART as unmasking of subclinical infection or, more commonly, later, as a consequence of nonadherence and/or ART failure [28, 30]. There is no sign of a reduction in the high mortality rates for HIV-associated cryptococcal meningitis, driven by late presentation, delayed diagnosis, and inadequate access to and efficacy of current antifungal medicines [31]. Though a number of HIV programs in South and Southeast Asia have achieved some success in terms of ART retention and early detection, the proportion of patients presenting to care with blood samples testing positive for cryptococcal antigen (CrAg) rival those seen in many settings in Africa, demonstrating that cryptococcal meningitis still presents a significant problem, even if absolute numbers of cases are lower [32–35].

Lack of R&D

A common misconception is that funding for cryptococcal meningitis comes under the umbrella of HIV. In reality, cryptococcal meningitis has fallen into a research and policy gap [4]. The research gap is most evident in drug development, as only 3 antifungal medicines—

amphotericin B, flucytosine (5-FC), and fluconazole—are currently used for the treatment of cryptococcal meningitis, all of which are decades old [21, 31]. Current WHO guidelines recommend 2 weeks of amphotericin B and 5-FC as the initial intensive induction phase, followed by a step-down to fluconazole for the consolidation and maintenance phases of treatment [36, 37]. However, this gold standard induction phase remains aspirational for most LMICs. Both amphotericin B and 5-FC are unavailable in the majority of LMICs, and the cheaper, more widely available fluconazole is an inadequate treatment for induction therapy [10]. In addition to patchy drug registration, amphotericin B is often not administered due to issues with toxicity (i.e., anaemia and renal impairment), poor laboratory monitoring facilities, cost barriers, and requirements for cold-chain shipment/storage at 4°C [31, 38]. Although there are 3 stringent regulatory authority (SRA)-approved generic manufacturers of 5-FC (Meda Pharm [recently acquired by Mylan], Sigmapharm, Valeant), none are currently registered in Africa [31, 38, 39, 40] despite compelling data for 5-FC's use in combination with either amphotericin B or fluconazole during the induction phase of treatment (regimens both recommended in the latest WHO guidelines [8, 14, 36, 37, 40]). Instead, fluconazole is widely available, well tolerated, and used for all phases of cryptococcal treatment despite clear evidence that fluconazole alone is a poorly effective medicine when used during the intensive induction phase, with 10-week mortality consistently >50% [8, 9, 10, 41].

R&D into the manufacture of new or improved therapies is currently inadequate. In 2015, R&D for cryptococcal meningitis totalled US\$5.8 million (just over 1% of the R&D budget afforded to tuberculosis [US\$567 million]), placing it in the bottom tier of neglected diseases, receiving support essentially from 3 public health funders: United States National Institutes of Health (NIH), United Kingdom Medical Research Council (MRC), and Australian National Health and Medical Research Council [3]. Funding for HIV/AIDS does not currently encompass OIs such as cryptococcal meningitis and, as yet, neither has it fallen under the umbrella of NTD funding. Very few new drugs for cryptococcal meningitis are in the human safety and dose-finding trial stage of development. VT-1129 and VT-1598 (Viamet Pharmaceuticals) are long-acting, azole-like compounds developed with assistance from the NIH's Therapeutics for Rare and Neglected Diseases programme. In vitro and animal models have demonstrated excellent activity and good oral pharmacokinetics, safety profile, and central nervous system penetration (www.viamet.com/pipeline.asp [42]). In addition, T-2307, which targets the fungal mitochondrial membrane, has completed initial human safety and dose-finding trials in the US (www.toyama-chemical.co.jp/en/rd/pipeline/index.html [43]). Oral formulations of amphotericin B (Matinas Biopharma) and compounds with activity against *Cryptococcus neoformans* (including AN 2690 [Anacor Pharmaceuticals], ASP 2397 [VICAL], and Ar 12 [Arno Therapeutics]) are currently only in preclinical stages of development. No additional new antifungal medicines have been developed for the treatment of cryptococcal meningitis in over 2 decades.

Strategies for control of cryptococcal meningitis

Despite the challenges, 2 strategies for the control and treatment of cryptococcal meningitis exist that together could make a significant impact: screen-and-treat programs for CrAg and delivery of short-course improved therapies [6]. CrAg screening of severely immunosuppressed patients (typically with CD4 counts ≤ 100 cells/mm³), which is recommended by the WHO and the President's Emergency Plan for AIDS Relief (PEPFAR), combined with pre-emptive antifungal treatment can prevent or detect at an early stage a significant proportion of cryptococcal meningitis cases, as the antigen can be detected in blood for weeks to months prior to the development of clinical disease. There are sensitive and specific CrAg lateral flow

assays (CrAg LFAs) that can be used for diagnosis either in the laboratory or at the point of care. The strategy is highly cost-effective and has recently shown a mortality benefit when combined with increased adherence support and early detection of tuberculosis (TB) [16, 44]. Although CrAg screening has been adopted into policy by over 20 countries, few have committed resources to implementing such programs; attention brought to cryptococcal meningitis as an NTD could help move such policy to action and begin saving lives.

With regard to treatment, optimized, sustainable regimens using existing antifungal medicines, drug development, and testing of repurposed drugs could significantly reduce the case fatality rate. Simplified treatment regimens consisting of short-course combination amphotericin B therapy and a purely oral combination of fluconazole and 5-FC are currently being tested in African LMICs with results expected in 2017 (ACTA trial, ISRCTN45035509). Liposomal formulations of amphotericin B offer a far better-tolerated alternative to traditional formulations. The AMBITION-cm trial is comparing the efficacy of 1 high dose of liposomal amphotericin in combination with fluconazole for HIV-associated cryptococcal meningitis (AMBITION-cm, ISRCTN10248064). A few intermittent doses could prove cost-effective if hospital admission duration was reduced, and there is precedent for efforts to increase access. In September 2016, Gilead extended a donation program to the WHO to make an additional 380,000 vials of liposomal amphotericin available at cost to continue treating patients with visceral leishmaniasis over 5 years [45]. If Gilead's program were expanded to cover cryptococcal meningitis, this could make improved, simplified treatment of meningitis far more accessible to resource-limited populations where disease burden is highest.

Repurposing of established drugs has also been applied to the search for new medicines [46]. This approach may expedite translation into clinical practice and reduce drug-development costs. Sertraline and tamoxifen are 2 such drugs that are fungicidal against *C. neoformans*, with good central nervous system penetration and synergy with fluconazole [30]. Both drugs are being studied separately as new adjunctive therapies for HIV-associated meningitis.

Lastly, raised intracranial pressure affects approximately one third of patients, and managing this common, debilitating, life-threatening complication improves patient outcomes [47, 48]. However, access to manometers, used to measure intracranial pressure, remains inadequate in LMICs and needs to be addressed alongside validation of simple measures to determine flow rates of cerebrospinal fluid (CSF) through spinal needles [49].

Consideration for inclusion in NTD list

Whilst debate continues as to whether cryptococcal meningitis should be listed as an NTD, affected persons in LMICs remain neglected, with opportunities missed to both prevent disease and provide effective treatment to reduce mortality. Stating that increased ART coverage alone will obviate the problem of HIV-associated cryptococcal meningitis in LMICs is not tenable; the evidence, with striking data from Botswana of ongoing cryptococcal meningitis cases despite excellent ART coverage, shows that this has not been the case to date [22]. Patients with advanced HIV-related cryptococcal meningitis will continue to present to hospitals in LMICs for the foreseeable future.

In 2013, the Cryptococcal Meningitis Action Group (CryptoMAG) was formed to improve access to diagnostic tests and essential antifungal medicines and to disseminate clinical best practices for treatment and prevention in LMICs. The debate over whether or not cryptococcal disease is an NTD detracts from cryptococcal meningitis being both HIV related and also urgently needing the interventions (funding, policy drives, and drug pipelines) from which NTDs benefit. We therefore call on the global health community, *PLOS NTDs*, UNITAID, The Global Fund, and WHO to declare cryptococcal meningitis an NTD and press for urgent

funding and policy drives to target optimisation and rollout of CrAg-screening programs, access to 5-FC and liposomal amphotericin B, and new drug development.

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CryptoMAG members: Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), Clinton Health Access Initiative (CHAI), Management Sciences for Health (MSH), Institut Pasteur, Global Action Fund for Fungal Infections (GAFFI), South Africa's National Institute for Communicable Diseases (NICD), and academic experts including from the University of Minnesota, University of Oxford, Liverpool School of Tropical Medicine, and St George's, University of London.

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