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## AIDS-related mycoses: the way forward

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### Abstract

The contribution of fungal infections to the morbidity and mortality of HIV-infected individuals is largely unrecognized. A recent meeting highlighted several priorities that need to be urgently addressed, including improved epidemiological surveillance, increased availability of existing diagnostics and drugs, more training in the field of medical mycology, and better funding for research and provision of treatment, particularly in developing countries.

### Keywords

HIV; AIDS; fungal infection; mortality; translational research; immunity

## Fungal infections in HIV patients

Fungi are often harmless in the context of normal host responses, but immune deficiencies, particularly in HIV-positive patients, result in significantly increased susceptibility to many fungal infections. The global defects in immune function resulting from HIV infection, in particular, cause susceptibility to several mucosal and life-threatening fungal diseases with pathogens such as *Candida*, *Cryptococcus*, and *Pneumocystis*. For example, it has been estimated that HIV/AIDS results in nearly 10 million cases of oral thrush and 2 million cases of esophageal fungal infections annually [1,2]. Of even greater concern is the high mortality associated with invasive fungal infections, which often exceeds 50%, despite the availability of antifungal drugs [2]. For example, the US Centers for Disease Control and Prevention (CDC) have estimated that there are approximately one million cases of cryptococcal meningitis globally every year in patients with HIV/AIDS with over 500 000 related deaths in sub-Saharan Africa in 2008 [3]. Although the accuracy of mortality estimates may be questionable, it is likely that fungal infections collectively kill about one and a half million

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people every year [1,2]. Thus, it is possible that at least as many people die from fungal diseases as tuberculosis (see <http://www.who.int/mediacentre/factsheets/fs104/en/>) or malaria (see <http://www.who.int/mediacentre/factsheets/fs094/en/>). Despite the huge burden and high mortality rates of fungal infections in HIV-infected patients, these diseases remain understudied and underdiagnosed compared with other infectious diseases [1,2].

## Priorities for the future

To address this burgeoning problem, over 80 participants from all over the world gathered for 3 days in July 2013 in Cape Town, South Africa for a meeting on AIDS-related mycoses (Figure 1). Plenary presentations at this conference covered topics including: the effect of HIV/AIDS on antifungal immunity; current limitations in diagnosis of these infections (particularly *Pneumocystis* in resource-limited settings); the epidemiology, surveillance, and public health aspects of these infections; the pathogenesis of fungal diseases (both from the host and pathogen perspective, including sessions on *Candida*, *Pneumocystis*, *Cryptococcus*, and other fungi); pathogenesis of fungal-related immune reconstitution inflammatory syndrome; and treatment options and the way forward (see the corresponding review [4] in this issue for more details on each of these topics). Considerable time was given to goal-directed general discussion during this meeting and six priorities for the immediate future were reached by consensus of all participants. These include:

1. Better epidemiological surveillance is needed because accurate estimates are unavailable for invasive fungal infections in HIV-infected patients globally.
2. There is a pressing need for better laboratory and point-of-care diagnostics and better availability of existing diagnostics for many fungal diseases. This is particularly true for *Pneumocystis jirovecii* pneumonia, for which the diagnostics available have limited sensitivity and availability (see [www.gaffi.org/wp-content/uploads/Pneumocystis-pneumonia-Fact-Sheet.pdf](http://www.gaffi.org/wp-content/uploads/Pneumocystis-pneumonia-Fact-Sheet.pdf)). Diagnostics need to be inexpensive, accessible, and simple for use in developing countries, such as the dipstick immunochromatographic test currently in use for the diagnosis of cryptococcal meningitis and for screening for antigenemia prior to the development of meningitis. Better diagnostics would facilitate aim (1).
3. We need better availability of existing drugs, particularly for *Cryptococcus*. Initial combination therapy with amphotericin B and flucytosine was recently shown to improve outcomes for cryptococcal meningitis [5], yet these drugs (especially flucytosine) are not readily available in many low- and middle-income countries, particularly in Africa, where there are high rates of mortality. These drugs need to be administered in combination for 2 weeks followed by fluconazole consolidation therapy. Antiretroviral therapy (ART) should be started 4–6 weeks after commencing anti-fungal therapy, to minimize the risk of mortality observed in recent trials of early introduction of ART [5].
4. More training in medical mycology (detection, diagnosis, and treatment) is needed, particularly in resource-limited settings where expertise and facilities for fungal identification are lacking. Access to relevant equipment is also required. An example is the benefit in reducing intracranial pressure during cryptococcal

meningitis by serial lumbar puncture, yet the equipment required to measure intracranial pressure, for example, a simple manometer, and relevant training in its use are lacking in most developing countries where this disease is endemic.

5. We need to stimulate funding in this area. Despite the high global burden of invasive mycoses, only 2–2.5% of infectious disease research budgets of the major funders in the UK and USA are targeted at human fungal infections [2]. There is an urgent need, in particular, for funding to implement programs aimed at better diagnosis, treatment, and surveillance of cryptococcosis in sub-Saharan Africa. Such programs could save tens of thousands of lives annually (Box 1). In addition to lobbying traditional funding agencies, we propose to:
  - i. Approach private philanthropic foundations.
  - ii. Submit a multi-European group application that focuses on critical issues in fungal diseases encountered in the developed and developing world.
6. We propose to maintain momentum within this field by establishing a working group on AIDS-related mycoses under the International Society for Human and Animal Mycology (ISHAM), hold a working group meeting at the ISHAM meeting in Melbourne in May 2015, and convene a second workshop on AIDS-related mycoses in Cape Town in 2016.

#### Box 1

##### **Better diagnosis, treatment, and surveillance of cryptococcosis in sub-Saharan Africa could save tens of thousands of lives annually**

Mortality is decreased by about 15% by the addition of flucytosine to amphotericin B [6]. If one conservatively assumes that 200 000 people per year are treated for cryptococcal meningitis in sub-Saharan Africa, then 30 000 lives would be saved if flucytosine were available. Additional lives could be saved by the wider availability of point-of-care, immunochromatographic dipstick tests to diagnose cryptococcosis in primary care clinics, lumbar puncture equipment to control intracranial pressure, and amphotericin B to use with flucytosine. Importantly, the long-term prognosis is excellent for patients who survive cryptococcal meningitis and are then treated with antiretroviral drugs [7]. Pre-ART screening for cryptococcal antigenemia in persons with CD4 < 100 cells/μl entering HIV care (prevalence rates of 4–12%) will also save costs in health systems and result in better outcomes [8].

### Concluding remarks

Fungal infections represent a major threat to individuals infected with HIV, particularly in developing countries. Greater funding and implementation of the approaches described here would have a significant impact and lead to substantial reductions in the morbidity and mortality associated with these diseases.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tim.2013.12.008.



**Figure 1.** Participants of the European Molecular Biology Organization (EMBO) workshop on AIDS-related mycoses held in July 2013 at the Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa.