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AIDS-Related Mycoses: Updated Progress and Future Priorities

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Serious fungal infections continue to devastate people living with HIV and remain a leading cause of infection-related deaths in this population, second only to tuberculosis. The third AIDS-related mycoses workshop updated progress in the field over the last 3 years and highlighted six key action points for the future.

Fungal Infections in Advanced HIV Patients

AIDS-related mortality has rapidly declined since 2003 owing to improved access to HIV testing and antiretroviral therapy (ART) [1]. However, this decline has slowed in recent years, attributed to the challenges of treating advanced HIV disease (defined by the World Health Organization as a CD4 count <200 cells/μl) [2]. Persons with advanced HIV disease remain susceptible to opportunistic infections and are at increased risk of death in the first year after starting ART. Although many people diagnosed with advanced HIV disease are ART-naïve, an increasing proportion are diagnosed after ART failure or following prolonged disengagement from care [3]. The risk of developing advanced HIV disease may be compounded by a surge in resistance to first-line ART medicines [3].

Since our previous meeting, cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia (PCP) remain the leading AIDS-related causes of mortality from fungal infection. These infection-related deaths are second only to tuberculosis, with the overwhelming majority of cases occurring in sub-Saharan Africa [4–6]. A recent systematic review estimated that the number of deaths caused by histoplasmosis in Latin America may be higher than tuberculosis deaths among people living with HIV [7]. In Southern China, a retrospective cohort study described the mortality caused by *Talaromyces marneffei* as the highest among all AIDS-associated complications [8]. Oral candidiasis remains a common cause of morbidity [9]. South Africa has the highest global prevalence of HIV infection, and associated with this, identification of emerging opportunistic fungi such as *Emergomyces africanus*. *Candida auris* now causes 14% of cases of candidaemia in South Africa [10]. HIV also increases the risk of death among patients with candidaemia (personal communication, N.P. Govender). Key action points from the previous two AIDS-related mycoses workshops were identified and summarized by Arunaloke Chakrabarti, the president of the International Society for Human and Animal Mycology (ISHAM), in his keynote address for the third workshop (Table 1) [11,12]. Since the previous workshops, significant progress has been made in the field as summarized below.

Recent Progress in the Field

Fungal infections remain an undeniable challenge for patients in resource-limited settings with advanced HIV disease. To address the issue of unacceptably high morbidity and mortality, promote discussion in the field, and to raise awareness of the lack of resources available for us to tackle these challenges, the first AIDS-related Mycoses workshop was launched in Cape Town in 2013. Considering the success of the second workshop in 2016, which reiterated the challenges that remain but also showcased promising progress in the field, we recently held the third AIDS-related Mycoses workshop. Fully subscribed for the first time, we hosted 120 participants from five continents in Cape Town, South Africa, in 2019 (Figure 1, and see Table S1 in the supplemental information online). While the remarkable progress made since the first workshop was presented, new and emerging challenges faced by healthcare professionals and researchers tackling these devastating diseases were emphasized. Major topics combined cutting-edge basic and clinical science, epidemiology, and public health and included: improving diagnosis of AIDS-related mycoses, host–pathogen interactions, immunology of fungal infections, treatment strategies and drug resistance, and new antifungal medicines and vaccines. The meeting concluded with an open discussion on future directions for the field. Great progress has been made in the diagnostics arena; this includes a highly successful cryptococcal antigen lateral-flow assay (CrAg LFA), a simple test that can be used in low-resource settings with minimal or no infrastructure. More recently, a *Histoplasma* antigen enzyme-linked immunosorbent assay (EIA) has been commercialized, with many countries now having access to this test [13]. Similarly, development of a new M1P1 antigen EIA for talaromycosis shows considerable promise and will hopefully be integrated into screening programmes for talaromycosis. Furthermore, the inclusion of some of the key diagnostics for fungal infections on the World Health Organization's *Model List of Essential in vitro Diagnostics* (EDL-2) is a tremendously encouraging step forward [14].

Recent clinical trials have provided important shifts in policy and guidelines. For example, the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial has already influenced a change in policy for the treatment of cryptococcal meningitis

Table 1. Summary of Action Points from Previous Meetings[a]

2013	2016	Progress
Better laboratory and point-of-care testing and access to current diagnostics	Better diagnostics and improved surveillance	*Cryptococcus* – CrAg test used in screening programmes and cross-sectional studies across sub-Saharan Africa has improved global estimates of disease burden [6]
Better epidemiological surveillance for HIV-related invasive fungal diseases		PCP – very little progress in simple rapid diagnostics, prevalence estimated in a systematic review of published studies [5] Endemics – *Histoplasma* EIA in Latin America will improve future burden of disease estimates. Very limited focus on Africa and histoplasmosis GAFFI has provided country-level estimates for many invasive mycoses
Improved access to existing drugs	Access to medicines, and development of new medicines and vaccines	Some improvement as mentioned below – largely driven through UNITAID/CHAI programme
Expansion of training for medical mycology in endemic areas		Through trials consortia, LIFE/GAFFI, PEPFAR
	Consolidation and extension of consortia for the delivery of multicentre clinical trials	Various *Cryptococcus* trials have been run through consortia. This infrastructure should be extended to other AIDS mycoses
Increased funding for development of diagnosis, treatment, and implementation programmes	Better collaborative working structures to accelerate translational medicine	
	Extension of current advocacy groups and public engagement	CryptoMAG has expanded over the last decade and AHD consortium now advocates for broader population of people with AIDS

[a]Abbreviations: AHD, Advanced HIV Disease Consortium; CrAg, cryptococcal antigen; CHAI, Clinton Health Access Initiative; CryptoMAG, Cryptococcal Meningitis Action Group; GAFFI, Global Action Fund for Fungal Infections; LIFE, Leading International Fungal Education; PEPFAR, President's Emergency Plan For AIDS Relief.

[15]. In this trial, 1 week of amphotericin B plus flucytosine, and 2 weeks of fluconazole plus flucytosine, were found to be efficacious induction treatment regimens in resource-limited settings. An overview of the AMBITION-CM trial, which will extend the work of the ACTA trial, was presented at the workshop [16]. This trial compares the efficacy of single high-dose liposomal-amphotericin B plus high-dose fluconazole and flucytosine compared with the current World Health Organization-recommended regimen, based on ACTA, of a 7-day course of amphotericin B deoxycholate plus flucytosine. David Boulware presented the proposed use of fosmanogepix (APX001) or oral amphotericin B for the treatment of cryptococcosis in a novel design and the ongoing ACACIA trial which is currently randomizing participants with cryptococcal antigenaemia to receive either liposomal amphotericin B plus fluconazole or fluconazole alone. There is a clear need for trials to optimize treatment for persons with cryptococcal antigenaemia who are now identified through large screening programmes in many more countries. Evidence for failures on fluconazole in this patient group was presented, and the need for a trial comparing the oral combination of fluconazole and flucytosine vs the current standard of fluconazole alone was highlighted. The meeting attendees noted that trials focused on *Talaromyces* infection are lacking and therefore require attention in the future.

Also encouraging is the progress made in country-level access to new diagnostics and medicines. Since our previous workshops, there has been an injection of funding from UNITAID, managed by the Clinton Health Access Initiative (CHAI), for an access programme for diagnostics and medicines in seven countries in sub-Saharan Africa. This access programme is focused on advanced HIV disease and related infections. Access to medicines includes established medicines where clinical trials have shown clear efficacy, for example, flucytosine. Here, new FDA approvals are decreasing generic flucytosine costs [17] but this is happening very slowly and needs continued pressure from advocacy groups. Many countries where antifungals are not widely available would use oral fluconazole monotherapy for cryptococcal meningitis which is far from optimal. Pfizer's Diflucan Partnership Program donates fluconazole for the treatment of cryptococcal disease in developing countries where HIV/AIDS is endemic. However, work needs to be done to ensure that generic fluconazole becomes more readily available to replace donated fluconazole. Liposomal amphotericin B will also be made more widely available through a Gilead access programme for cryptococcal meningitis. There is also a need to prioritize access to new agents, such as SUBA-itraconazole, as they become available.

Key Priorities for the Future

At the third AIDS-related Mycoses workshop the following six priorities were highlighted for the immediate future:

i. Increased human resource capacity for AIDS-related mycoses at both the

Figure 1. Participants of the Third AIDS-Related Mycoses Workshop Held at the AFGrica Medical Mycology Research Unit at the Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa, in July 2019.

clinical and basic science levels. There are two aspects to consider here:

- Training courses for clinicians and scientists in high-burden and resource-limited areas to provide updates on current knowledge, research, and clinical trials.
- Advanced training and support for postdoctoral and early career researchers interested in pursuing a career in medical mycology. Increasing the capacity of research groups in high-disease burden settings will enhance support provided for interested graduate students attending courses described above. Furthermore, these efforts could include promoting interest in pharmacokinetics, an area in medical mycology with exceptionally limited expertise.

ii. Improved access to diagnostic tests and antifungal medicines for AIDS-related mycoses. Many new and improved diagnostic tests and medicines have been developed, but access to these is still severely lacking in low- and middle-income countries. For example, Nigeria and other African countries have no access to CrAg screening tests for cryptococcal disease. Similarly, access to a new commercial *Histoplasma* EIA should be expanded. Furthermore, translating work from clinical trials through implementation science and investigating ways to ensure access to new medicines for a large population in rural areas is a priority. Better management and distribution of available diagnostics and medicines are an urgent need.

iii. Screening of AIDS-related fungal pathogens beyond *Cryptococcus*. Lessons learnt from CrAg screening could be applied to other mycoses, including those caused by *Histoplasma* and *Talaromyces*. The evidence provided by clinical trials should lead to implementation of real-world screen-and-treat programmes. This has been demonstrated by the success of CrAg screening programmes. Therefore, clinical trials should be planned both to optimize treatment for CrAg-positive patients and for other fungal diseases to provide evidence for mortality reduction with screening.

iv. A better understanding of personalized medicine with the use of host-directed therapy. There are two aspects here: firstly, the host response, and secondly, drug interactions. There is a need to understand the host response to infection to identify and target specific host components that could be used to treat infection. Furthermore, understanding drug interactions and pharmacokinetics in specific patients will improve treatment strategies in patients receiving ART.

v. Consolidation and extension of consortia for the delivery of multicentre clinical trials. This point remains a key priority identified in 2016. While there are major groups working in the area of cryptococcal meningitis, better cohesion and extension to other AIDS-related mycoses will enable more rapid progress in this area. Coordinated multicentre clinical trials will provide a pipeline to patient populations for easier distribution of new drugs and diagnostic tests.

vi. Increased focus on advocacy for AIDS-related mycoses. The extension of current advocacy groups and public engagement is maintained as a key

priority for the field. Areas that have a proven track record can be utilized and implemented into rural areas. An AIDS-related mycoses twitter feed (twitter: @AIDSMycoses) will provide a platform to help coordinate these efforts and keep the community connected between meetings.

Concluding Remarks

Fungal infections continue to cause significant mortality and morbidity in people with advanced HIV disease. A concerted effort has been made to improve the availability of current medicines and diagnostics. Together with new antifungal medicines, promising clinical trial results, new diagnostic tests for neglected pathogens, and improved advocacy at an international level, the outlook for saving lives is encouraging. Despite this progress, many areas need improvement such as the consolidation of clinical trial networks and expanding the availability of important diagnostics and new treatments. Screening and preemptive treatment of patients most at risk for fungal infection would not only save lives but also have an overall cost benefit by preventing serious illness. Finally, and of high importance, is the need to build human capacity in the field. This has been highlighted in both previous workshops and again in this workshop. Building capacity requires training programmes to create awareness, advanced training programmes to improve skills, and programmes that support basic scientists and clinical researchers interested in pursuing a research career in medical mycology.

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Spotlight

Phagocytosis in a Shape-shifting Bacterium

Lucie Gallot-Lavallée[1] and John M. Archibald[1,*]

Phagocytosis – cell ingestion – is an important process confined to eukaryotes. Or is it? Shiratori *et al.* have discovered the existence of phagocytosis in a planctomycete bacterium, raising new questions about the significance of phagotrophy beyond the realm of eukaryotic life.

The ability to engulf large particles, including entire cells, by phagocytosis is thought to be restricted to eukaryotic organisms. Phagocytosis is in fact often considered to have played a role in the evolution of eukaryotic cellular complexity by providing the means with which to ingest bacteria (and thus give rise to mitochondria and chloroplasts by endosymbiosis). In a recent