

AIDS-Related Mycoses: Current progress in the field and future priorities

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Abstract

Opportunistic fungal infections continue to take an unacceptably heavy toll on the most disadvantaged living with HIV-AIDS, and are a major driver for HIV-related deaths. At the second EMBO AIDS-Mycooses Workshop, clinicians and scientists from around the world reported current progress and key priorities for improving outcomes from HIV-related mycoses.

Key words

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

Global burden of HIV-related fungal disease

Whilst many fungi cause low grade superficial infections, these microorganisms are a major cause of high-mortality invasive infections in immunocompromised individuals[1]. Advanced HIV infection continues to be a major driver for invasive fungal diseases, despite the global scale-up of antiretroviral therapies (ART)[1]. Defining the global burden of fungal diseases presents a major challenge, as they are often insidious in nature, and there are intrinsic challenges in their diagnosis, as well as a global lack of capacity for fungal diagnostics[1]. Best estimates suggest there are up to a million invasive fungal infections per annum related to HIV-AIDS (primarily cryptococcosis, pneumocystosis, histoplasmosis, and talaromycosis (formerly penicilliosis)), with a consequent mortality of up to 500,000 per annum [2]. This places HIV-related fungal disease at

57 nearly the same level of mortality as other major infectious diseases such as malaria and
58 tuberculosis[3, 4]. Current case fatality rates for cryptococcal meningitis vary between 30% and
59 70% for patients diagnosed and treated in sub-Saharan Africa[5, 6]. Recent data from the Amazon
60 region for HIV-associated histoplasmosis indicates a 50% overall mortality rate at 1 year[7].
61 Studies in Uganda indicate on overall mortality of around 20% for HIV-related *Pneumocystis*
62 pneumonia[8], and a mortality rate of 28% for HIV-associated talaromycosis in Viet Nam[9]. In
63 addition, oral candidiasis is very common and associated with a high degree of morbidity if
64 untreated[1].

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66 The Joint United Nations Programme on HIV/AIDS (UNAIDS) has established an ambitious
67 treatment target known as 90-90-90 to control the AIDS epidemic(ii). But even if these targets are
68 reached, there will still be a substantial burden of fungal disease in patients who present for care
69 late or disengage from or fail ART. Despite this, fungal disease has not had the same level of focus
70 from the global community, although as a result of recent efforts from the medical mycology
71 community, we hope this is now changing.

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73 At the inaugural meeting of the EMBO AIDS-Mycoses Working Group in Cape Town, South Africa
74 in July 2013, 5 key goals were identified to improve outcomes from these deadly diseases:

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76 1. Better epidemiological surveillance for HIV-related fungal diseases.
77 2. Better laboratory and point-of-care testing.
78 3. Improved access to existing drugs.
79 4. Expansion of capacity for medical mycology training.
80 5. Increased funding for development of diagnosis, treatment and implementation programmes,
81 especially in resource-poor settings.

82 83 **Recent progress in the field**

84 As part of ongoing efforts to stem the tide of fungal disease, over 100 researchers spearheading
85 the battle against HIV-related fungal diseases in Africa, Asia, North and South America, Europe
86 and Australasia met at the 2nd EMBO AIDS-Mycoses Workshop for three days in July 2016 in
87 Cape Town, South Africa, to discuss current progress in the field and future priorities.

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89 The workshop was notable for the geographic breadth of participants, as well as excellent
90 coverage for all the major HIV-related fungal diseases. The major topics discussed were
91 epidemiology and public health, diagnostics, host-pathogen interactions, immunology, drug
92 resistance, treatment strategies, new antifungal drugs, and vaccines. Detailed updates were given
93 on epidemiology and public health aspects of the major AIDS-related mycoses including
94 cryptococcosis, histoplasmosis, talaromycosis and pneumocystosis. In addition, newly recognized
95 HIV-associated invasive fungal infections due to *Emmonsia* spp. (recently renamed *Emergomyces*)
96 were highlighted. These infections appear to be unique to Southern Africa, and the clinical
97 presentation mimics disseminated histoplasmosis. A notable observation was that whilst
98 antiretroviral roll out appears to have had some impact on the incidence of cryptococcal meningitis
99 in recent years, half of all cases occur after ART has been established[10]. When taken in the
100 context of the global failure to reduce new HIV infections, emerging HIV drug resistance and
101 challenges in retaining patients in ART care in resource-limited settings, it is clear that the ongoing
102 epidemic of cryptococcal meningitis will be sustained. The high rates of HIV-associated infection
103 and mortality from histoplasmosis in Latin America and talaromycosis in South and South East
104 Asia were also highlighted[9, 11]. Key highlights in fundamental research in AIDS-related mycoses
105 included genomics-based studies of cryptococcal evolution and resistance in the host, a number of
106 studies detailing aspects of metabolic adaptation of *Cryptococcus neoformans* and *Talaromyces*
107 *marneffeii* in the host, and descriptions of the latest discoveries in understanding the innate and
108 adaptive immune responses to *Pneumocystis* spp.

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110 A number of advances in the development and implementation of point-of-care-based testing
111 (POCT) strategies were highlighted during the meeting. In particular, there has been enormous
112 progress with the implementation of cryptococcal lateral flow device-based screening programmes

113 in sub-Saharan Africa. South Africa has recently implemented national reflex laboratory screening
114 with a projected 250 000 persons estimated to be screened per annum[12]. The strategy of treating
115 antigen-positive patients reduces the likelihood of future cryptococcal meningitis[13]. Further
116 progress was also reported with the development of rapid tests for *Talaromyces marneffe* and
117 *Histoplasma capsulatum* infection.

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119 Access to currently available antifungal medicines as well as the development of novel antifungal
120 drugs is an urgent priority, due to the limited drug classes and emerging resistance to triazoles.
121 Planned recruitment to the AMBITION study was outlined (intermittent high dose AmBisome
122 [liposomal amphotericin B] on a high dose fluconazole backbone for cryptococcal meningitis
123 induction therapy in sub-Saharan Africa), as well as current Phase 1/2 studies for VT-1129, a new
124 oral agent for cryptococcal disease, progress of the ACTA trial (oral fluconazole plus flucytosine or
125 one week amphotericin B-based therapy versus two weeks amphotericin B-based therapy) and the
126 ASTRO trial (Adjunctive Sertraline for the Treatment of HIV-associated cryptococcal meningitis).
127 There continues to be inadequate access to flucytosine, amphotericin B and itraconazole in
128 countries with major burdens of either cryptococcal meningitis or endemic mycoses. The
129 emergence of triazole resistance in both *Cryptococcus neoformans* and *Aspergillus fumigatus* was
130 also discussed[14, 15]. Notable progress has been made in understanding the genetic basis for the
131 emergence of cryptococcal heteroresistance during therapy, and combination antifungal strategies
132 to limit this.

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134 Advocacy for fungal diseases continues to gather pace, through the Global Action Fund for Fungal
135 Infections(GAFFI) (i), the Cryptococcal Meningitis Advocacy Group(CryptoMAG) (iii), and the
136 planned establishment of new groups focused on pneumocystosis and histoplasmosis. Whilst
137 CryptoMAG successfully proposed the addition of flucytosine and amphotericin B to the essential
138 medicines list, recent attempts to include itraconazole, a crucial drug for histoplasmosis,
139 talaromycosis, and aspergillosis, on the WHO(World Health Organisation)'s essential medicines list
140 have been unsuccessful. Furthermore, none of these AIDS-related mycoses are currently
141 classified as neglected tropical diseases by the WHO.

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143 **Key priorities for the future**
144 During the meeting, there was a major focus on discussing the key priorities to move the field
145 forward, and 5 priorities were identified:

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147 1. **Better collaborative working structures for basic scientists and clinical researchers to
148 accelerate translational medicine.** The meeting itself acted as an environment in which basic
149 scientists and clinical researchers intensively interacted. Promoting greater interaction in the
150 future will lead to accelerated translation. The 3rd AIDS-related Mycoses Conference is planned
151 in 3 years' time.
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153 2. **Better diagnostics and improved surveillance.** It is particularly apparent that without POCTs
154 for the major AIDS-related mycoses these infections remain difficult to diagnose, and treat, and
155 their true global burden remains very difficult to ascertain.
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157 3. **Access to established medicines, as well as development of new medicines and
158 vaccines.** Access in particular to flucytosine, amphotericin B, and itraconazole are particularly
159 patchy, and liposomal amphotericin B (Ambisome) remains very expensive in many countries.
160 Acceleration of vaccination programmes should be a key priority, but will be challenging due to
161 the difficulties in eliciting immune responses in immunocompromised people.
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163 4. **Consolidation and extension of consortia for the delivery of multi-centre clinical trials.**
164 Whilst there are major groups working in the area of cryptococcal meningitis, better cohesion
165 and extension to other AIDS-related mycoses will enable more rapid progress in this area.

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167 5. **Extension of current advocacy groups and public engagement.** New advocacy groups are
168 being established, based on CryptoMAG, covering histoplasmosis and pneumocystis. GAFFI is
169 currently supporting the Kenyan government in an ambitious 5-year development program(ii).
170

171 **Concluding remarks**

172 Invasive fungal infections continue to be a major cause of mortality in the context of advanced HIV
173 infection globally. The medical mycology community made significant recent progress in delivering
174 novel diagnostic and therapeutic strategies to limit mortality from these infections, and there are
175 some encouraging novel therapies on the horizon. However, engagement of major funding bodies
176 and governmental and non-governmental organizations is urgently needed to enable substantial
177 reductions in the unacceptably high morbidity and mortality from the AIDS-related mycoses.
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179 **Resources**

- 180 i. <http://www.unaids.org/en/resources/documents/2014/90-90-90>
181 ii. <http://www.gaffi.org>
182 iii. <http://preventcrypto.org/about-us/>
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