The Global Action Fund for Fungal Infections
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Open Letter - Disseminated histoplasmosis and AIDS

To the World Health Organisation, UNAIDS, Pan-American Health Organisation, Médecins Sans Frontières, Bill and Melinda Gates Foundation, Drugs for Neglected Diseases Initiative, UNICEF, national public health agencies and governments.

February 2016

Dear Key Stakeholder in tackling the AIDS epidemic,

A recent rough estimate of disseminated histoplasmosis in AIDS is 100,000 cases worldwide and 80,000 deaths, mostly due to lack of diagnosis and partly unavailability of treatment. If the UNAIDS target of reducing AIDS deaths to under 500,000 is to be achieved, action needs to be taken now on disseminated histoplasmosis.

Disseminated histoplasmosis in AIDS is well recognised in the USA where awareness, laboratory capacities and access to effective antifungal therapy are all fully developed. In Central and South America, and in Africa and SE Asia, it is usually undiagnosed or misdiagnosed as tuberculosis.

A group of institutions from the Americas recently declared HIV-associated histoplasmosis a neglected disease described as: "an invisible elephant out of the radar of International Health authorities, organizations and funders". They estimated that histoplasmosis was responsible for 1 in 5 AIDS-related deaths in the Americas, more or at least equivalent to the burden of HIV-tuberculosis and 100 times more than malaria (view article)

A few current examples: the median age of cases in Panama is 33 years, and 59% of these patient die. In Manaus, Brazil, the age range of cases is 12-42 years, with an overall mortality of 48%, and in the Northeast of this country, a burden of 208 cases of disseminated histoplasmosis in AIDS patients was detected in a period of 4 years, with 42% fatal.

Histoplasmosis is an airborne infection related primarily to bat and bird guano exposure in soil. There are particular 'hot spots' mostly identified in the Americas, but it is a worldwide pathogen, with cases described in most African countries, SE Asia, India and China. It is grossly under-diagnosed because of the low sensitivity (average 50%) of stained smears and the slow growth of organism in special medium culture (which is not available in many locations). In AIDS, the culture usually becomes positive after the patient has died (10-21 days). The unavailability of even culture and microscopy in many countries,

contributes to difficulties in case identification and prompt treatment initiation. A briefing document is here.

Rapid diagnosis with antigen testing and PCR are excellent; results can be provided in under 24 hours. We profiled this in the '95-95 by 2025' Roadmap issued in May 2015 (page 5). An antigen testing kit is commercially available from IMMY, and they are field testing a point of care *Histoplasma* antigen test, which will take about an hour for diagnosis. Other companies are also working on this. PCR is not commercially available, but could be with the right purchase incentives, and is done routinely in Spain, Colombia, Argentina, Guatemala, and French Guiana.

Treatment works well. Amphotericin B and itraconazole are the drugs of choice with 87-100% response rates in AIDS in the USA. Liposomal amphotericin B (Ambisome) is probably more effective in very ill patients, but needs further study and an access program, like leishmaniasis. The effectiveness of fluconazole is very low. The new agent posaconazole (and probably isavuconazole) is probably highly effective and needs to be evaluated.

Itraconazole is widely available (see country distribution on the map). Low doses work for histoplasmosis. It is too costly for weeks of therapy for most patients, and daily cost varies substantially. There is a significant itraconazole interaction with NNRTIs, notably efavirenz, and uncertainty about dosing. Rifampin use with itraconazole renders itraconazole useless (induction of metabolism) and so histoplasmosis co-infection with TB is problematic to manage. Studies need to be done to address these interactions, which need funding.

For very ill patients, amphotericin B is preferable. Unfortunately this is not as widely available as it should be (see map). Amphotericin B is also required for optimal treatment of cryptococcal meningitis, another common cause of death in AIDS.

Areas of high endemicity can be identified with skin testing surveys, as shown here Current maps are not very precise, in most countries, even in the Americas, with the exception of the USA. There are no maps for Asia, with the exception of China and the current map for Africa is by country, rather than locality. Hot spots can be mapped using skin testing, so that diagnostic efforts can be geographically focused. There is only one current supply of skin testing reagent – from an academic department in Mexico City.

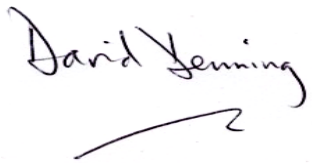
Numerous issues were identified at an international workshop on disseminated histoplasmosis in AIDS recently held in Suriname (www.gaffi.org/histoplasmosis-the-leading-aids-diagnosis-in-the-guiana-shield-and-parts-of-central-america/). The participants (from French Guiana, Suriname, Guyana, Venezuela, Trinidad, Panama, Guatemala, Mexico, Brazil, Argentina, Colombia, USA and UK) identified several structural changes to address the problems. Examples were: Those centers without antigen diagnosis have mortality rates of 45-60% (if the diagnosis is made at all), and those with antigen, 7-30% mortality; Guyana and some other countries do not have amphotericin B or itraconazole, so the disease is untreatable there. Listing these drugs on their country Essential Medicine List could accelerate access. Laboratory capacity is inadequate for fungal diseases throughout the Caribbean

and many central American countries.

Histoplasmosis doesn't only affect AIDS patients. It can affect people without underlying conditions and other immunocompromised patients, and the chronic cavitary form can mimic pulmonary TB (a cause of 'smear negative TB'). Even when AIDS is conquered, histoplasmosis will continue to pose problems, so improved diagnosis and therapy is required as part of capacity strengthening in very many countries. Notably many patients present with disseminated histoplasmosis with rising CD4 counts months after starting therapy, so antiretroviral therapy alone is not enough to deal with the problem.

The above mentioned morbidity and mortality burden demands action of all stakeholders to realize the following measures:

1. To enable direct, rapid access to reliable and practical diagnostic tests in all areas where histoplasmosis occurs or is suspected;
2. To define the real extend of morbidity and mortality of histoplasmosis so as to define all histoplasmosis endemic areas in the world;
3. To bring therapy for histoplasmosis within the reach of all who need it, especially in endemic areas
4. To stimulate scientific investigation on histoplasmosis epidemiology, diagnosis and treatment
5. To organize regular conferences and educational sessions concerning histoplasmosis with support for those living in endemic areas to participate and enable disease awareness amongst treating physicians.



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