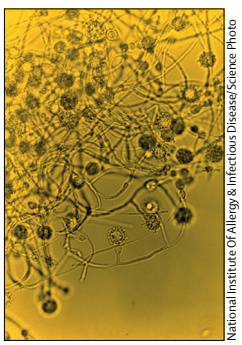
# Histoplasmosis dethrones tuberculosis in Latin America

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Tuberculosis is one of the most prelevant diseases worldwide. Data from the WHO showed that in 2016,[1] 10·4 million new cases of tuberculosis occurred globally. In patients with AIDS, tuberculosis is a leading cause of death.[1] In the past two decades, diagnosis of tuberculosis has improved markedly, with tests such as interferon-γ release assays, GeneXpert MTB/RIF, and lateral flow urine lipoarabinomannan assay. Despite most physicians being aware of the possibility of a particular patient having tuberculosis, alternative diagnoses are frequently not considered. In this scenario, questions such as, "What if this patient does not have tuberculosis?" should be as important as "Could this be tuberculosis?". Antoine Adenis and colleagues[2] have identified that histoplasmosis can no longer be seen as a coadjuvant disease compared with tuberculosis in patients with AIDS in South and Central America.

Adenis and colleagues[2] built their argument by studying retrospective data from several data banks, including the percentage of intradermal test reactivity to histoplasmin in diverse geographic areas, the annual incidence of HIV-associated histoplasmosis, and the general mortality rate in Latin America during the year 2012 compared with data on HIV-associated tuberculosis. The authors showed that the mortality and incidence rates associated with histoplasmosis were equivalent if not superior to tuberculosis in patients with AIDS in the region. Although histoplasmosis is probably the most prevalent endemic systemic mycosis in Latin America, its real burden remains to be determined because of the paucity of prospective epidemiological studies. Conversely, the estimated burden of AIDS-associated histoplasmosis has been detailed at the country level for the first time, indicating the countries in which the disease should be under the public heath surveillance radar.

Histoplasmosis is usually diagnosed during the late stages of disease in Latin America. Although the higher frequency of skin disease in disseminated histoplasmosis in Latin America (about 50% *vs* about 15% in the USA) could be related to generic variations in *Histoplasma capsulatum*,[3] leading to a high fungal skin tropism in Latin America, late diagnosis is probably a better explanation. Diagnosis of histoplasmosis in Latin America typically occurs after 14–21 days, when the fungus is recovered in culture. In the USA, diagnosis can occur as early as 2–5 days after clinical manifestations by detection of *Histoplasma* spp antigen in urine. *Histoplasma* spp antigen is not commercially available in most Latin America centres (available in only 13·2% of centres in Brazil [unpublished]). The misdiagnosis of AIDS-associated histoplasmosis was previously reported[4] in Cameroon (central Africa), where several patients with AIDS and presumed tuberculosis automatically received antituberculosis therapy, although tuberculosis was never confirmed. Post-mortem examination finally detected disseminated histoplasmosis in many of these patients.[4]

In addition to a poor disease awareness, the late diagnosis and the limited access to less toxic antifungal drugs, such as liposomal amphotericin B (L-AmB), help to explain why the mortality of disseminated histoplasmosis is about three-times higher in Latin America than in the USA.

What are the additional aims of the histoplasmosis international community? First, is to increase disease awareness, which has been nicely achieved by Adenis and colleagues.[2] Second, is to have better diagnosis tools available (*Histoplasma* spp antigen detection). Last, is to have better drugs in place, particularly L-AmB, which in a randomised double-blind trial[5] had superiority over deoxycholate amphotericin B, with a survival benefit. Similarly to leishmaniasis, a single high-dose (about 10 mg/kg) of L-AmB could be as efficacious as a 3 mg/kg dose of L-AmB given for 14 days, which might be a less toxic and cheaper strategy and deserves a proper randomised controlled trial.

Adenis and colleagues' Article,[2] our Comment, and a Review[6] published in *The Lancet Infectious Diseases*, are all in close synchrony with the Global Action Fund for Fungal Infections (Gaffi) initiative. Gaffi is a non-profit organisation based in Switzerland that aims to identify and publicise gaps in diagnostics and treatments for fungal diseases. Most endemic mycoses remain neglected in the global perspective, including histoplasmosis. Even though *H capsulatum* is a major threat to Latin America, histoplasmosis is now known as a global disease with hundreds of cases being reported outside the region, particularly in China, India, Japan, Australia, and the African continent. Now is the time for

histoplasmosis to be recognised as one of the leading causes of death in patients with AIDS.

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We declare no competing interests.

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