

Disseminated histoplasmosis in Central and South America, the invisible elephant: the lethal blind spot of international health organizations

The neglected histoplasmosis in Latin America Group

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Nowhere to be seen

Histoplasma capsulatum is endemic in the Americas [1,2]. It has been an AIDS-defining infection since 1987 [3]. In the USA, it is a well known pathogen that can be promptly diagnosed and treated. In South and Central America, and may be the Caribbean, it is another story. Since the onset of the HIV epidemic, there have been a number of convergent reports that suggest that disseminated histoplasmosis is one of the major AIDS-defining infections and a major killer of HIV-infected patients [4–8]. However, most hospitals still have no way of diagnosing the disease and often lack the best treatments for the disease. There is thus a double tragedy, with clinicians failing to diagnose what is killing their patients, and public health authorities failing to tackle one of the major burdens of disease. Mycologic diagnosis rests on direct examination and culture of tissue samples that is often invasive and may take weeks to reveal *H. capsulatum* [9]. Molecular biology is not commercially available and thus not available in most hospitals. The detection of *H. capsulatum* antigens in urine or serum by enzyme immune assays remains a simple, noninvasive, sensitive method, with an increasing number of alternatives that are being evaluated but are still distributed on a small scale in Latin America [9]. The future diagnostic tests that could radically change the picture should be ASSURED,

that is affordable, sensitive, specific, user friendly, rapid, equipment free, and delivered to those who need it [10].

Connecting the dots

Histoplasmin skin test studies show how widespread histoplasmosis is [1,2]. Mycologists have long been aware that the disease is there, but they often do not receive samples from clinicians in charge of HIV patients. Therefore, reports mention that a large proportion of histoplasmoses are HIV positive. However, this perspective is not likely to enhance histoplasmosis in HIV programmes. A more fruitful question, and one whose answer should get clinicians, public health authorities, and international authorities to act is how does histoplasmosis rank compared with other opportunistic infections? or what proportion of AIDS cases are in fact histoplasmosis cases? To answer requires sustained collaboration between mycologists and HIV clinics. A few teams have answered this question – in Panama, 7.65% of patients with HIV infection had culture-positive *H. capsulatum* [6]; in Guatemala, histoplasmosis is the second opportunistic infection just after tuberculosis, but with a greater mortality [8]; in Venezuela, before the highly active antiretroviral therapy era, among 200

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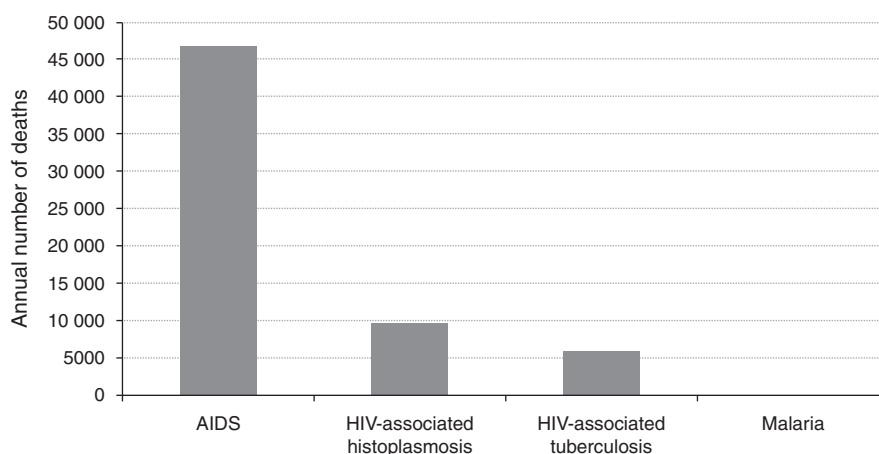


Fig. 1. Estimated number of deaths per year for different major infectious diseases in Latin America.

patients with AIDS, histoplasmosis was diagnosed in 43 (21.5%) [7], and in one study it was documented in 29 of 66 (44%) autopsies performed [1]; in Fortaleza Brazil, in 378 consecutively admitted HIV patients, 164 (43%) had disseminated histoplasmosis [5]; in French Guiana, histoplasmosis is the first AIDS-defining infection and has long been the first cause of AIDS-related death [4,11]; and a recent study showed that 42% of HIV patients admitted with CD4⁺ cell counts less than 200 and 85% of those with CD4⁺ cell counts less than 50 had disseminated histoplasmosis [12]. One may argue that these are focal hotspots of histoplasmosis; however, this does not fit with the spread of endemic regions for histoplasmosis. On the contrary, if one connects the dots, the picture is staggering.

Histoplasmosis inflating tuberculosis statistics

Reducing tuberculosis deaths, and notably HIV-associated tuberculosis, is a major objective for the Joint United Nations programme on HIV/AIDS (UNAIDS), the Pan American Health Organization (PAHO), and numerous AIDS programmes. Recently, data from Latin America showed a 60% increase in culture-negative relative to culture-positive tuberculosis [13]. The conclusion was that culture-negative cases were possibly because of other causes. Presumably, a large proportion of these deadly cases were disseminated histoplasmosis misdiagnosed as tuberculosis [14,15].

A staggering invisible burden

There are an estimated 1 600 000 HIV patients in the Americas. If we apply the incidence rate of 1.5 per 100 person-years measured in French Guiana [4], this suggests

that there are 24 000 histoplasmosis cases in the Americas per year. The historical death rate of 40% [16] of deaths in histoplasmosis would mean there are 9600 deaths per year. In addition, it is arguable that the incidence rate is a low estimate of that of other regions in the Americas. Indeed in this French territory, 30% of patients have less than 200 CD4⁺ cell counts when tested and over 85% of the patients are on treatment, a situation that is probably more favourable than in other countries where up to 60% of patients are at stage C, where treatment initiation is still delayed and a large proportion of the HIV population is not yet on antiretroviral treatment [17]. In addition, for undiagnosed histoplasmosis, mortality is likely to be far greater than 40%. For the Americas, the estimated annual number of malaria deaths for 2013 was 84 [18]; HIV-tuberculosis annual deaths are estimated 6000 [19], and AIDS, without specification, is estimated 47 000 annual deaths [17]. So the number of deaths from tuberculosis in AIDS patients is at a similar level than HIV-associated histoplasmosis deaths (Fig. 1). However, one is a strategic objective of UNAIDS/PAHO/the CDC/GATES foundation's HIV/AIDS strategic plans, and the other is nowhere to be seen.

How could 9600 deaths a year – approximately the equivalent number of deaths as 70 Boeing 737 plane crashes a year – have gone unnoticed? The extrapolation of this to the 34 years since the AIDS epidemic was recognized puts the cumulated number of deaths in Latin America well over 100 000. We concede that such estimates are gross approximations, that histoplasmosis incidence may be more heterogeneous than we portray, but the order of magnitude is plausible.

Correcting the lethal blind spot

The fact that a network of independent HIV care and mycology specialists reaches the same conclusion should

be taken seriously. So far, the scattered scientific publications do not seem to have percolated up towards the upper spheres of public health decision making. The expanding and earlier access to antiretroviral treatments should have a substantial impact on the mortality of histoplasmosis [20,21]. However, despite efforts to promote early HIV testing and to put greater numbers of persons on antiretroviral treatment, histoplasmosis still has a bright future because late testing, adherence and follow-up difficulties are still common.

The international public health system and numerous HIV programmes have a blind spot; we believe a huge global health tragedy has been overlooked, and apathy to change when the stakes are so high would be unacceptable. Mycology is a neglected specialty [22], often struggling to keep functioning; innovation is hampered by financial anaemia. Recently, PAHO has funded technical cooperation on histoplasmosis at a level of 50 000 dollars, a good start but it represents less than one dollar per estimated histoplasmosis death.

We need simple diagnostic tests, and we need to lobby for affordable liposomal amphotericin B in endemic countries, teach clinicians to adapt diagnostic and treatment algorithms and get histoplasmosis on board of the HIV/AIDS strategic plans. Surely, major funders have the power to make things right, by funding and inciting national AIDS programmes to correct this gap and avoid more unnecessary deaths.

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Conflicts of interest

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