Perspective Piece

How Many Have Died from Undiagnosed Human Immunodeficiency Virus–Associated Histoplasmosis, A Treatable Disease? Time to Act

Mathieu Nacher,* Antoine Adenis, Christine Aznar, Denis Blanchet, Vincent Vantilcke, Magalie Demar, Bernard Carme, and Pierre Couppié

Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane CIC-EC CIE 802, Cayenne General Hospital, Cayenne, French Guiana; Coordination Regionale de la Lutte Contre le VIH de Guyane, Laboratoire Hospitalo-Universitaire de Parasitologie Mycologie, Unité des Maladies Infectieuses et Tropicale, et Service de Dermatologie Vénéréologie, Centre Hospitalier de Cayenne, Cayenne, French Guiana; Equipe EPaT EA3593 Epidemiologie des Parasitoses et Mycoses Tropicales, Université Antilles Guyane, Cayenne, French Guiana

Abstract. Human immunodeficiency virus (HIV)–associated disseminated *Histoplasma capsulatum capsulatum* infection often mimics tuberculosis. This disease is well known in the United States but is dramatically underdiagnosed in Central and South America. In the Amazon region, given the available incidence data and the regional HIV prevalence, it is expected that, every year, 1,500 cases of histoplasmosis affect HIV patients in that region alone. Given the mortality in undiagnosed patients, at least 600 patients would be expected to die from an undiagnosed but treatable disease. The lack of a simple diagnostic tool and the lack of awareness by clinicians spiral in a vicious cycle and made a major problem invisible for 30 years. The HIV/acquired immunodeficiency syndrome community should tackle this problem now to prevent numerous avoidable deaths from HIV-associated histoplasmosis in the region and elsewhere.

In the Guianas and the Amazon Basin, the prevalence of human immunodeficiency virus (HIV) is approximately 1%. There have been some decreases in incidence in some states in this region, but recent increases in incidence in northern states of Brazil have been reported.^{1–3} The population of the Amazon basin is estimated to be approximately 10 million persons,⁴ which would imply that approximately 100,000 persons are HIV positive in the Amazon Basin.

The Amazonian environment is suitable for the growth of *Histoplasma capsulatum*.⁵ For immunocompetent patients, this organism causes mostly benign infections, but in severely immunodepressed HIV-infected patients, infection with this organism leads to a fatal disease in the absence of diagnosis and treatment. There lies the problem. Clinical symptoms are unspecific and often mimic those of tuberculosis.^{6,7} Diagnosis is difficult and requires invasive procedures (biopsies, bone marrow smears), and trained staff to detect *H. capsulatum*, often after weeks of culture.⁸ Severe infections are often fatal within days.⁹ However, death often occurs after long delays in which patients are unsuccessfully treated for unconfirmed tuberculosis. Patients die because they are not treated for a treatable disease and because there is no diagnosis test. With no diagnosis, this possibility is not included in the diagnostic and treatment algorithms of clinicians who, despite unknowingly encountering this disease on a regular basis, have never seen a case because it was never diagnosed. In this context, then why give presumptive treatment of a disease that is not present?

It is tragic but it makes total sense. It is even frighteningly tragic when one crunches the numbers to estimate what it means that after 30 years of the HIV epidemic, one of the leading causes of acquired immunodeficiency syndrome (AIDS) in the Amazon¹⁰ still goes largely unrecognized and evolves under the radar of national plans and international funding efforts.

The only incidence data available for this region suggests that the incidence of histoplasmosis during the highly active antiretroviral therapy era was 1.5 cases/100 person-years.¹⁰

The historical mortality rate of disseminated histoplasmosis was > 30% despite mycology expertise.^{7,8} This finding indicates that for 100,000 HIV patients, there would be 1,500 cases of histoplasmosis/year and 600 deaths/year, and probably more if undiagnosed. This finding also indicates that for more than 30 years the cumulated death rate in the region must have been huge, in the tens of thousands.

A rational sceptic could rightly doubt this claim from the generalization of data from the smallest South American territory to the entire Amazon and elsewhere. However, when one reviews the literature, it becomes evident that histoplasmosis is present throughout the region, this fact has been known for decades, and that we should have been paying more attention.⁵ The high prevalence of histoplasmin test reactivity in the region was known even before AIDS was identified in 1981.¹¹ Histoplasmosis has been an AIDS-defining illness since 1993. We should have connected the dots earlier.

How could something so huge escape the attention of the HIV/AIDS community in the region? One explanation for this dramatic blind spot is that in the region, the diagnostic capacity for mycology has been insufficient. It has been long argued that medical mycology is a neglected area of biology, and that the often low incidence of mycoses is caused by a lack of medical mycologists rather than the absence of the mycoses.¹² Another explanation is that the standard conceptualization of HIV/AIDS, the usual indicators, and the Joint United Nations Programme on HIV/AIDS terminology and framework did not explicitly entail disseminated histoplasmosis or the regional AIDS-defining illnesses. The anesthetic effect of the familiarity of vertical concepts and vertical programs can make it difficult to reframe the problem and see what was always there.

For better diagnostic and treatment, we should know what AIDS is to direct diagnostic hypotheses when caring for individual patients. Misdiagnosing histoplasmosis as tuberculosis, not only delays a life-saving treatment of the individual patient, but it can confound tuberculosis statistics (incidence, resistance, mortality) and make it difficult to evaluate tuberculosis program results.

The current financial difficulties should not stand in the way of building the diagnostic capacity for detection of histoplasmosis.

*Address correspondence to Mathieu Nacher, Centre Hospitalier de Cayenne, Rue des Famboyants, Cayenne 97300, French Guiana. E-mail: mathieu.nacher@ch-cayenne.fr

It does not necessarily cost much to do the diagnosis. Treatment relies on amphotericin B for severe forms and itraconazole for non-severe forms and prophylaxis.⁷ Both drugs are generic drugs that are perfectly affordable. The toxicity of amphotericin B leads industrialized countries to use the costly liposomal version of the drug. However, The Drugs for Neglected Disease Initiative is releasing a cheap alternative that was developed for treatment of cryptococcosis.¹³ This is an opportunity for resource-limited countries in disease-endemic areas for treatment of histoplasmosis. We should not wait any longer. Every year wasted to build capacity for diagnosis and treatment of histoplasmosis in the Amazon Basin and elsewhere leads to hundreds of deaths that could have been avoided. This is not acceptable.

Received April 27, 2013. Accepted for publication June 5, 2013.

Published online November 25, 2013.

Authors' addresses: Mathieu Nacher, Centre Hospitalier de Cayenne, Rue des Flamboyants, Cayenne 97300, French Guiana, E-mail: mathieu.nacher@ch-cayenne.fr. Antoine Adenis, Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane, INSERM DGOS CIE 802, Cayenne General Hospital, Avenue des Flamboyants, Cayenne 97306, French Guiana, E-mail: antoine.adenis@ch-cayenne.fr. Christine Aznar, Service Hospitalo Universitaire de Parasitologie Mycologie, Centre Hospitalier de Cayenne, Cayenne, French Guiana, E-mail: christine.aznar@ch-cayenne.fr. Denis Blanchet, Laboratoire Hospitalo Universitaire de Parasitologie Mycologie, Centre Hospitalier de Cayenne, Cayenne, French Guiana, E-mail: denis.blanchet@ch-cayenne.fr. Vincent Vantilcke, Service de Médecine, Centre Hospitalier de l'Ouest Guyanais, Saint Laurent du Maroni, French Guiana, E-mail: v.vantilcke@ch-ouestguyane.fr. Magalie Demar, Department of Infectious and Tropical Disease, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana, E-mail: magalie.demar@ch-cayenne.fr. Bernard Carme, Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane, CIE INSERM 802, Pole de Guyane, Centre Hospitalier de Cayenne, Cayenne, French Guiana, E-mail: bernard.carme@ch-cayenne.fr. Pierre Couppié, Equipe EA 3593, Epidemiologie des Parasitoses et Mycoses Tropicales, Université des Antilles et de la Guyane, Cayenne, French Guiana, E-mail: couppie.pierre@voila.fr.

REFERENCES

1. Cohen J, 2006. HIV/AIDS: Latin America and the Caribbean, South America. *Science* 313: 484.
2. Nacher M, Vantilcke V, Parriault MC, Van Melle A, Hanf M, Labadie G, Romeo M, Adriouch L, Carles G, Couppie P, 2010. What is driving the HIV epidemic in French Guiana? *Int J STD AIDS* 21: 359–361.
3. Brazil MoHo, 2012. *Boletim Epidemiológico Aids e DST, 2012 Report*.
4. OAS States, 2005. *Amazon River Basin*.
5. Colombo AL, Tobon A, Restrepo A, Queiroz-Telles F, Nucci M, 2011. Epidemiology of endemic systemic fungal infections in Latin America. *Med Mycol* 49: 785–798.
6. Krug ES, Glenn HR, 1948. Comparative studies in tuberculosis and histoplasmosis among 2000 students entering Pennsylvania State College, September, 1947. *J Lancet* 68: 206–208.
7. Couppie P, Aznar C, Carme B, Nacher M, 2006. American histoplasmosis in developing countries with a special focus on patients with HIV: diagnosis, treatment, and prognosis. *Curr Opin Infect Dis* 19: 443–449.
8. Huber F, Nacher M, Aznar C, Pierre-Demar M, El Guedj M, Vaz T, Vantilcke V, Mahamat A, Magnien C, Chauvet E, Carme B, Couppie P, 2008. AIDS-related *Histoplasma capsulatum* var. *capsulatum* infection: 25 years experience of French Guiana. *AIDS* 22: 1047–1053.
9. Couppie P, Sobesky M, Aznar C, Bichat S, Clyti E, Bissuel F, El Guedj M, Alvarez F, Demar M, Louvel D, Pradinaud R, Carme B, 2004. Histoplasmosis and acquired immunodeficiency syndrome: a study of prognostic factors. *Clin Infect Dis* 38: 134–138.
10. Nacher M, Adenis A, Adriouch L, Dufour J, Papot E, Hanf M, Vantilcke V, Calvez M, Aznar C, Carme B, Couppie P, 2011. What is AIDS in the Amazon and the Guianas? Establishing the burden of disseminated histoplasmosis. *Am J Trop Med Hyg* 84: 239–240.
11. Hay RJ, White HS, Fields PE, Quamina DB, Dan M, Jones TR, 1981. Histoplasmosis in the eastern Caribbean: a preliminary survey of the incidence of the infection. *J Trop Med Hyg* 84: 9–12.
12. Ajello L, 1971. The medical mycological iceberg. *HSMHA Health Rep* 86: 437–448.
13. Initiative DND, 2012. *Alternative Formulations of Amphotericin B*.